

EPIDITHIA-2,5-PIPERAZINEDIONES: TOTAL  
SYNTHESES OF THE HYALODENDRINS.

by

ROBERT MICHAEL WILLIAMS

B.A. Syracuse University  
(1975)

SUBMITTED IN PARTIAL FULFILLMENT  
OF THE REQUIREMENTS FOR THE  
DEGREE OF

DOCTOR OF PHILOSOPHY

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

(JUNE, 1979)

© Massachusetts Institute of Technology, 1979

Signature of Author.. Department of Chemistry May 25, 1979

Certified by.....  
s Supervisor

Accepted by.....  
Chairman, Department Committee

Archives

MASSACHUSETTS INSTITUTE  
OF TECHNOLOGY

JUN 7 1979

LIBRARIES

EPIDITHIA-2,5-PIPERAZINEDIONES: TOTAL  
SYNTHESES OF THE HYALODENDRINS.

by

ROBERT MICHAEL WILLIAMS

Submitted to the Department of Chemistry  
on May 25, 1979 in partial fulfillment of the requirements  
for the Degree of Doctor of Philosophy.

ABSTRACT

A synthesis of the antiviral, antifungal antibiotic (+)-hyalodendrin (53) and the corresponding bis-dethio(methylthio) derivative (+)-gliovictin (52) is described. Sarcosine anhydride was monoformylated to form 1,4-dimethyl-3-formyl-2,5-piperazinedione (183) in high yield. Protection of the hydroxyl group of (183) was realized by conversion to the O-t-butyldiphenylsilyl ether (211). Benzylolation of the enolate of (211) afforded benzyl derivative (217). Sulfenylation of the enolate derived from (217) with monoclinic sulfur in THF afforded mercaptan (243). The mercapto group of (243) was protected as its methyl disulfide and the silyl protection removed by acidic hydrolysis to afford enolic methyl disulfide (246). Sulfenylation of (246) with triphenylmethyl dithio chloride in the presence of triethylamine followed by reduction with sodium borohydride and oxidation with  $\text{KI}_3$  py afforded (+)-hyalodendrin in 11% overall yield from sarcosine anhydride. The synthetic hyalodendrin was identical to the natural material by  $^1\text{H}$  NMR, IR, MS, TLC and combustion analysis.

(+)-Gliovictin was synthesized by sulfenylation of (183) with methyl sulfenyl chloride in the presence of triethylamine in THF to afford methylthio carboxaldehyde (212). Reduction of the aldehyde to alcohol (213) followed by protection of the hydroxyl group as the t-butyldimethylsilyl ether afforded (214). Sulfenylation of the enolate derived from (214) with methyl disulfide afforded dimethylthio diastereomers (215). Stereoselective benzylolation of the enolate derived from (215) followed by hydrolysis of the silyl protection afforded (+)-gliovictin in 38% overall yield from sarcosine anhydride.

The stereoselection observed in these and other sulfenylations is thought to be due to steric shielding of the enolate by pseudo-axially disposed mercapto functionalities across the ring caused by an anomeric effect.

Preparation of 1,4-dimethyl-3-formyl-6-mercapto-6-benzyl-2,5-piperazinedione (180) resulted in the formation of the tautomeric bicyclic hemimercaptals (261). Attempts to sulfenylate (261) with subsequent conversion to hyalodendrin were made without success.

William H. Rastetter, Assistant Professor

This doctoral thesis has been examined by a Committee  
of the Department of Chemistry as follows:

Professor Daniel S. Kemp.....*Daniel S. Kemp*.....  
Chairman  
Professor William H. Rastetter.....*William H. Rastetter*.....  
Thesis Supervisor  
Professor George H. Büchi.....*G. H. Büchi*.....

<u>CONTENTS</u>	<u>Page</u>
Abstract.....	2
Dedication.....	5
Acknowledgement.....	6
Abbreviations.....	10
Part I: Introduction	
Naturally Occurring Epidithiapiperazinediones.....	11
Physical Properties and Characteristic Chemistry of Epipolythiapiperazinediones.....	32
Synthetic Studies.....	40
Total Syntheses.....	53
Part II: Discussion	
Prolylproline Anhydride Studies.....	64
Total Synthesis of Hyalodendrin and Gliovictin....	72
Part III: Experimental.....	121
References.....	189
Biographical Sketch.....	204

## DEDICATION

This thesis is dedicated to my loving wife  
Janet Wilma Reisinger  
Her encouragement, support, understanding,  
fathomless patience and love made the completion  
of this thesis possible and worthwhile.

The only Zen you find  
on the tops of mountains  
is the Zen you bring up there.

## ACKNOWLEDGEMENT

## ACKNOWLEDGEMENTS

The author wishes to fully acknowledge the following people who provided invaluable assistance in the quality and creation of this thesis. Dr. George M. Strunz of the Canadian Forestry Service was kind enough to provide samples of natural hyalodendrin, bisdethio(methylthio) hyalodendrin and a full set of spectral data on the natural products. Prof. David N. Harpp of McGill University was extremely helpful in providing many experimental details on the sulfur transfer reagents, samples of such, and many helpful suggestions. Dr. Catherine Costello and Andy Shkuta of the MIT mass spectral facility (K. Biemann principal investigator) provided invaluable assistance in the recording and interpretation of high resolution mass spectra. Jean Owens recorded the low resolution mass spectra and Jim Simms of the MIT Spec Lab provided a great deal of help with the recording of NMR spectra. Bob Digiacomo created many, fine pieces of glassware that made the experimental work more enjoyable and efficient. The author is grateful to Prof. George M. Whitesides for providing a pre-print of a full paper on thiol-disulfide exchange reactions and also for very kindly furnishing employment recommendations, encouragement and useful suggestions. Thanks are also extended to Prof. Frederick D. Greene for showing an interest in this work, many helpful discussions and also for employment recommendations. Numerous other people on the MIT staff were helpful and thanks are extended to them.

The author is especially grateful to the people in the Rastetter research group who provided friendship, encouragement and many forms of assistance. In particular, Larry Nummy was extremely helpful, especially during the earlier phases of this work in providing technical and scientific insight that was instrumental in the author's scientific development.

Tom Erickson was invaluable for instruction and recording of FT NMR spectra and provided a very amicable sports environment. Tony Chancellor ran many high quality 270 MHz NMR spectra and thanks are extended to her for this assistance. Of course, Mike Venuti, Tom Gadek, John Frost, Jeff Tane, Dennis Phillion and Julian Adams all deserve special recognition in providing friendship, entertainment and encouragement that made the frustrating times more bearable and the good times that much more enjoyable.

The author is especially indebted to William H. Rastetter for providing the author with the independence and scientific freedom to pursue interesting possibilities, and at the same time, affording gentle guidance with a seemingly infinite supply of patience. The enthusiasm, interest and encouragement provided by WHR made the graduate experience and production of this thesis particularly rewarding. Prof. Rastetter was extremely competent at providing financial support from 1976 until the present time. The author is indebted to the Department of Chemistry for providing financial assistance in the form of a teaching assistantsship for 1975-76.



The author also wishes to thank Vera Spanos for typing and assistance in preparation of this thesis.

Abbreviations

BI	benzimidazole
m-CPBA	meta-chloroperbenzoic acid
DIPEA	diisopropylethylamine
DKP	diketopiperazine
DMF	dimethylformamide
DIBAL	diisobutylaluminum hydride
DMSO	dimethylsulfoxide
DTNB	5,5'-dithiobis(2-nitrobenzoic acid)
HPLC	high pressure liquid chromatography
im	imidazole
LDA	lithium diisopropylamide
MsCl	methanesulfonyl chloride
NBS	N-bromosuccinimide
Phth	phthalimido
py	pyridine
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
EtoAc	ethyl acetate
MeOH	methanol
EtOH	ethanol
DME	dimethoxyethane
Et <sub>2</sub> O	ethyl ether
i-PrOH	isopropanol

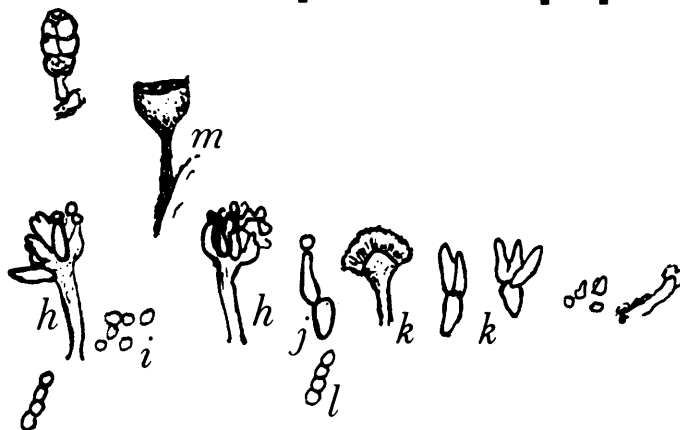


**Naturally**



**Occurring**

**Epidithiapiperazinediones**

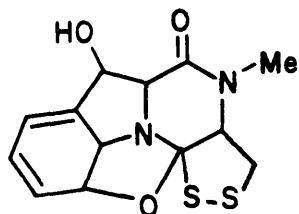


## FUNGAL FLORA KNOWN TO PRODUCE EPIPOLYTHIAPIPERAZINEDIONES

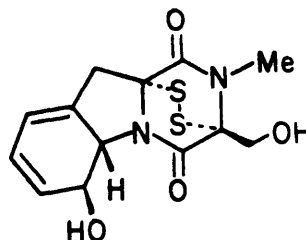
(illustrated on preceeding page) ref.6a

1. Chaetomium cochliodes
  - a) perithecium
  - b) terminal hairs
  - c) spores
  - d) ascus
2. Pithomyces chartarum
  - e) conidia and mycelium on rye grass
  - f) conidia from potatoe dextrose cultures
  - g) spent condiophores, mature conidia on rye grass
3. Penicillium terlikowski Zaleski
  - h) representative penicilli
  - i) mature conidia
4. Aspergillus Terreus Thom
  - j) vesicle and sterigmata
  - k) primary and secondary sterigmata
  - l) conidia
  - m) stalk and base of colyptrate conidial mass

In 1936, Weindling reported on the isolation of a fungal growth inhibiting metabolite produced by Trichoderma viride.<sup>1</sup> This yellow, crystalline substance was at first thought to have structure 1.<sup>2,3</sup>



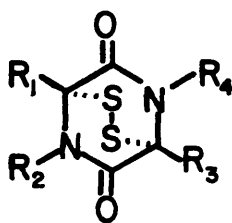
1



2

However, it was not until 1958 when Johnson and Woodward<sup>4</sup> proposed the correct structure for this substance called gliotoxin 2. The absolute stereochemistry was later elucidated by x-ray analysis.<sup>5</sup> Gliotoxin is also produced by other microorganisms including Penicillium terlikowskii, Aspergillus fumigatus, Aspergillus terreus and Gliocladium fimbriatum.<sup>6a-d</sup>

Since the discovery of gliotoxin, many other mould metabolites have been isolated and shown to possess a bridge of sulfur atoms across a 2,5-piperazinedione ring.<sup>6a-d</sup> This unique ring system 3,



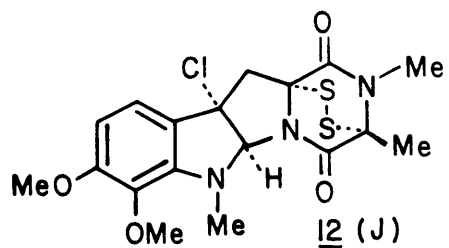
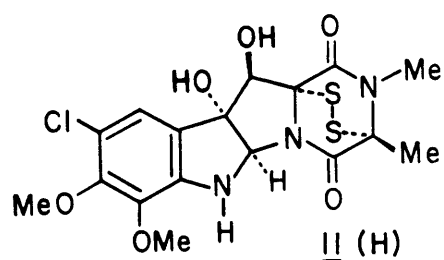
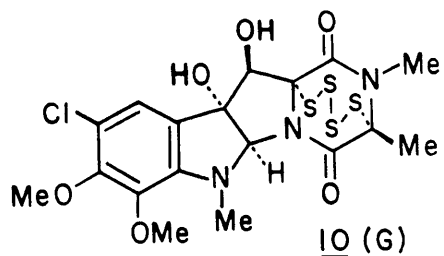
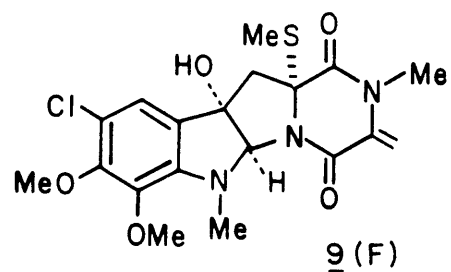
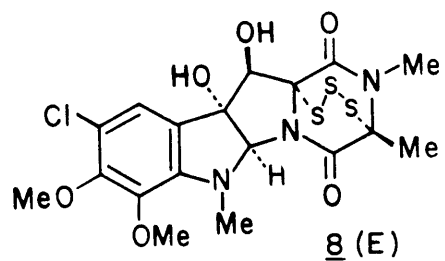
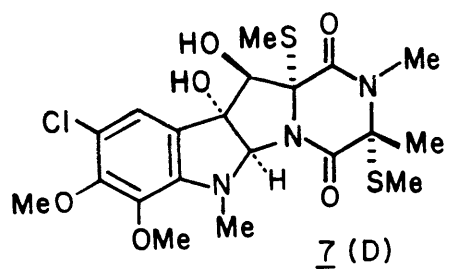
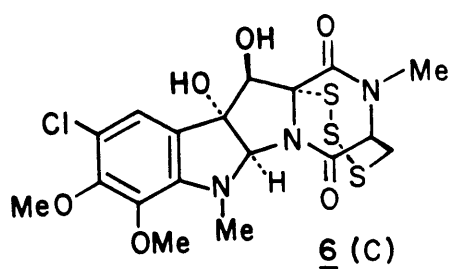
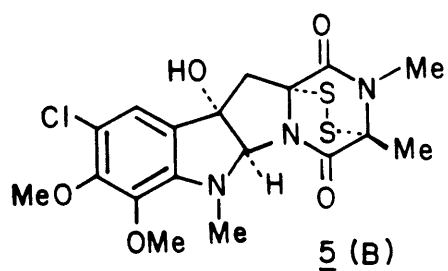
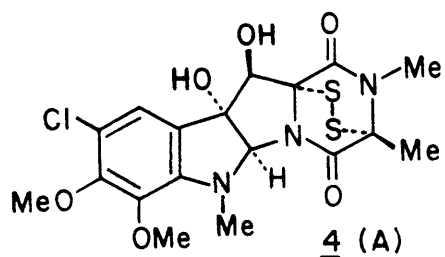
3

has been shown to be the site responsible for the potent antiviral, antifungal, antibiotic, antitumor and cytotoxic properties which the class displays.<sup>6a-d</sup>

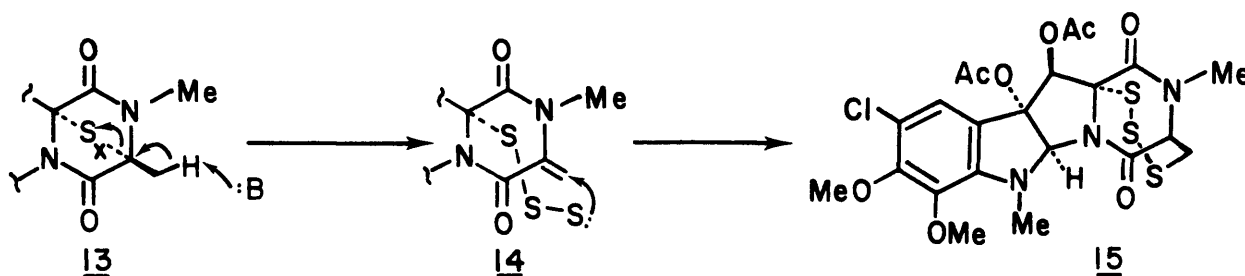
In the following section, the structures of the naturally occurring epidithia-2,5-piperazinediones and their naturally occurring derivatives are presented. With each family of compounds, mention is made of some of the more outstanding physiological properties displayed. Chemists have suggested interesting schemes to explain the fungal biogeneses of these complex metabolites. The more intriguing of these will be illustrated along with the discussion of the appropriate family.

The natural habitat of the organisms known to produce epidithia-2,5-piperazinediones are soils and most of these are found in temperate and subtropical regions of the earth. There is good evidence that the fungi produce these toxic metabolites in their natural environment. This has been studied most intensively in New Zealand, where Pithomyces chartarum causes the serious disease in sheep known as facial eczema.<sup>6a-d</sup> Pithomyces chartarum has been shown to produce a family of toxic metabolites known as the sporidesmins.<sup>9</sup> Sporidesmins A-J (4-12) have been isolated and characterized. Sporidesmins D (7) and F (9) have been shown to lack the antibacterial properties that the epipolysulfides possess. Some interesting chemical correlations have been achieved in this series. Sporidesmin E (8) can be converted to sporidesmin A (4) by reaction with 1 equivalent of triphenylphosphine.<sup>9g</sup>

## Sporidesmins



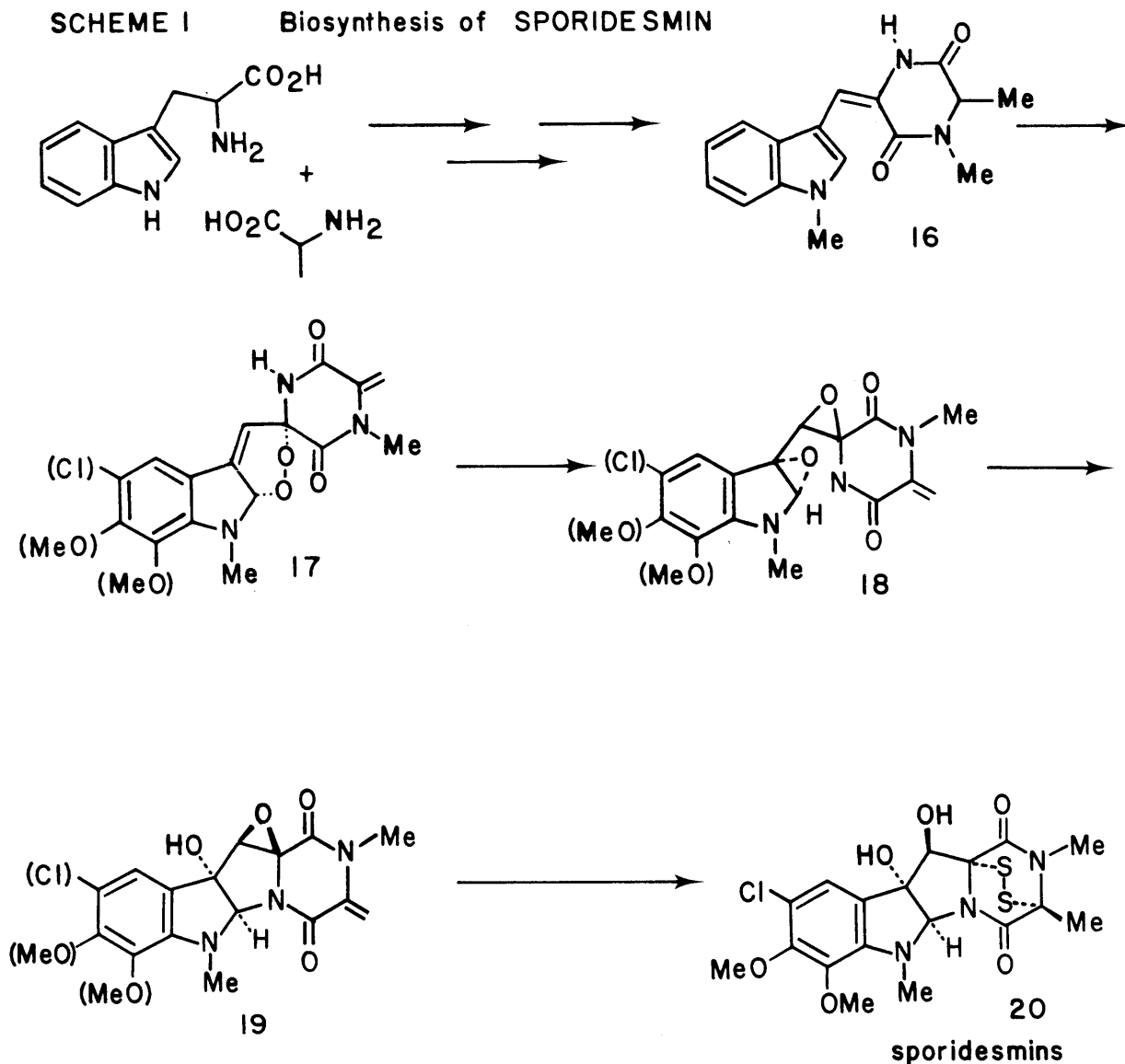
The tetrasulfide, sporidesmin G(10) can be prepared from either 4 or 8 by reaction with hydrogen polysulfide in chloroform<sup>9f</sup> or dihydrogen disulfide.<sup>9h</sup> Treatment of sporidesmin A (4) with methyl iodide, pyridine and sodium borohydride affords sporidesmin D (7). The most unusual member of the sporidesmin family is perhaps sporidesmin C (6). The structure of sporidesmin C was deduced from mass spectral evidence on the corresponding diacetate, produced by heating the metabolite in acetic anhydride and pyridine. Sammes has suggested<sup>6b</sup> that sporidesmin C diacetate is an artefact produced by the precedented elimination and readdition of sulfur across the dehydrodipeptide system (i.e. 13  $\rightarrow$  14  $\rightarrow$  15) during acetylation.



Relatively little work has been carried out on the biogenesis of the sporidesmins. Sammes proposed a possible



## SCHEME 1 Biosynthesis of SPORIDESMIN

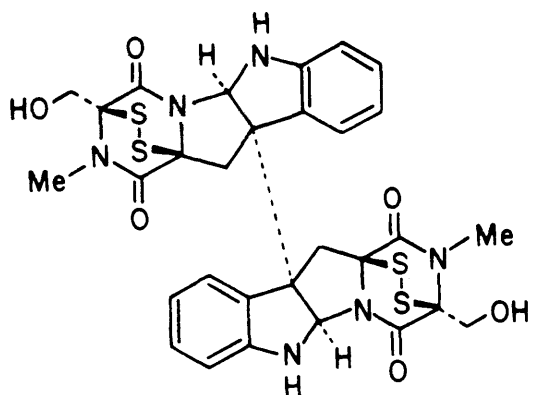


biosynthetic scheme involving a well-precedented oxidative ring closure of a tryptamine derivative to produce the eserine ring system (SCHEME 1, 18→19) present in the sporidesmins. It is interesting to note the oxidation state of 19, which would permit the introduction of the sulfur atoms as sulfur nucleophiles. Sulfur introduction in vivo is not well understood, and will be discussed later.

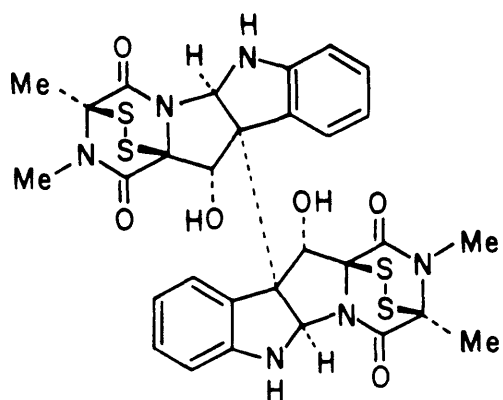
An interesting family of dimeric indole alkaloids containing the epidithia-2,5-piperazinedione moiety have recently been isolated and characterized. These include chaetocin,<sup>10a-c</sup> the verticillins<sup>11a-c</sup> and the melinacids.<sup>12a,b</sup> X-ray analysis<sup>10b</sup> and C.D. studies have shown that these compounds are antipodal with respect to the epidithia-2,5-piperazinedione moieties compared to gliotoxin, aranotin and the sporidesmins. It is interesting to note that these compounds, in general, lack the antiviral activities displayed by the gliotoxins and sporidesmins. This family does, however, display antimicrobial activity against gram positive bacteria, but are inactive against gram negative species and fungi. Verticillin A (22) also showed considerable anti-tumor properties<sup>11b</sup> against HeLa cells ( $ED_{50}$   $0.28\text{ml}^{-1}$ ). The in vivo antibacterial properties of these metabolites have been shown<sup>12b</sup> to be ineffective; these compounds also exhibited high toxicity in test animals.

While little has been done on the biogenesis of these unusual compounds, the dimeric indole alkaloid skeleton is presumably formed via oxidative coupling of tryptamine derivatives. This type of coupling has been demonstrated in the laboratory and is illustrated in Hinos recent synthesis<sup>13</sup> of follicanthine (30) and chimonanthine (31) (SCHEME 2)

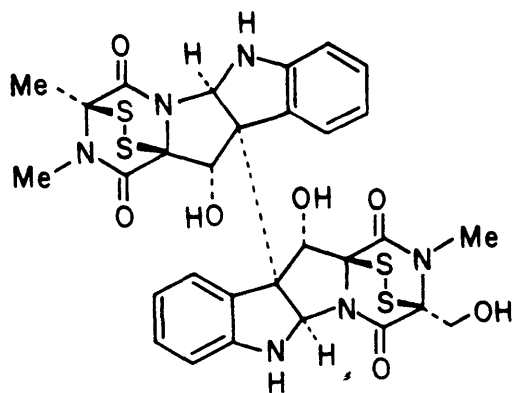
## Indolic Dimers



chaetocin 21

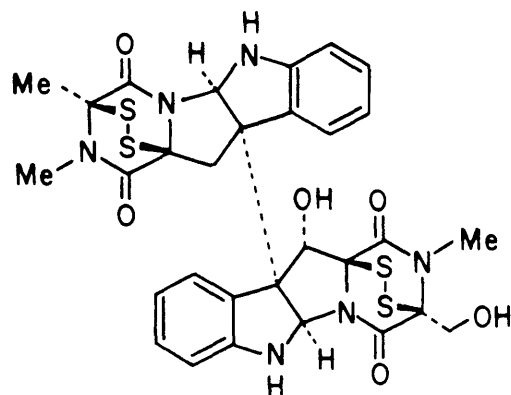


verticillin A 22

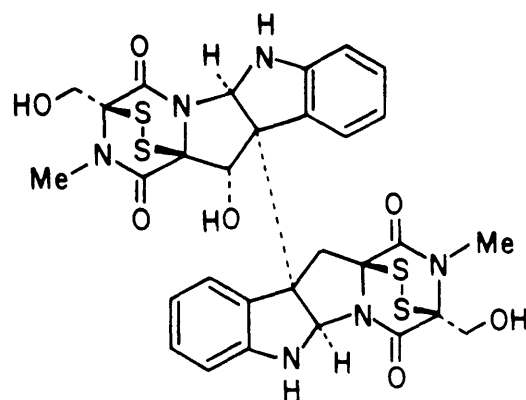


verticillin B 23

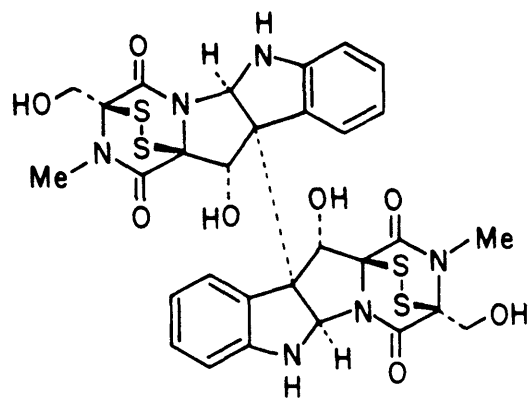
verticillin C 24 (S5 analog of B)



melinacidin II 25



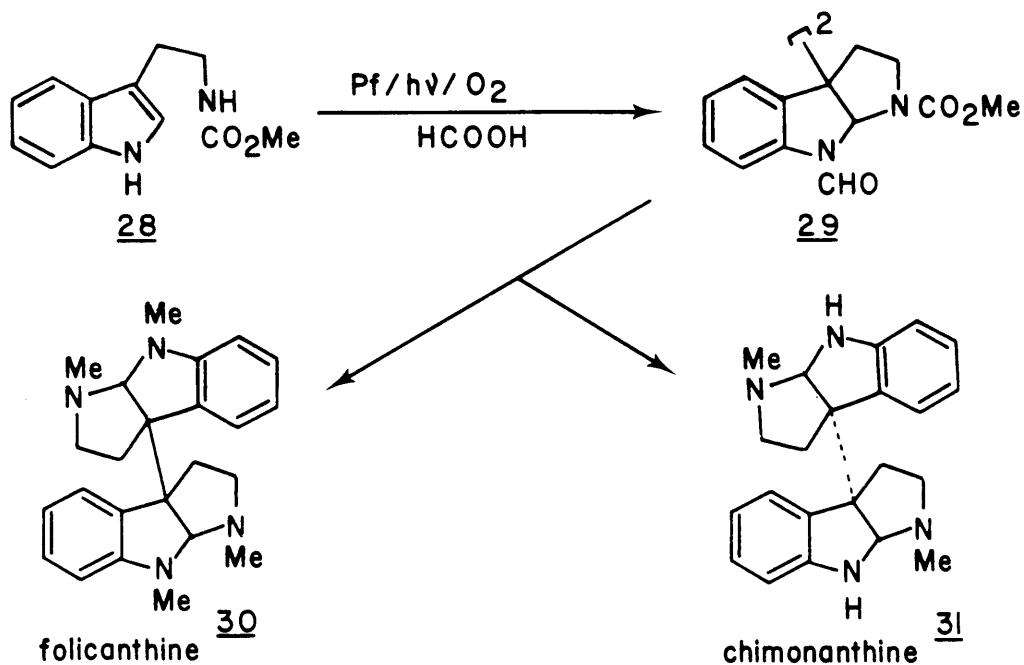
melinacidin III 26



melinacidin IV 27

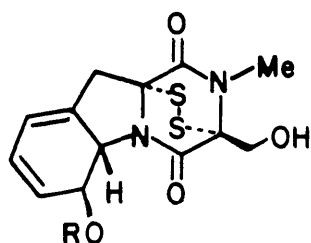
IIa-IIa'-dihydroxychaetocin

## SCHEME 2



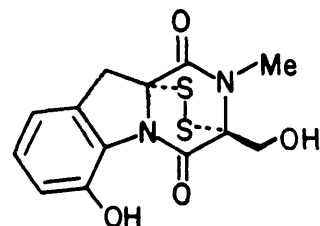
The gliotoxins (2,32,33) and aranotins (34-38) have stimulated a greater amount of synthetic, biosynthetic and pharmacological interest than any other family of epidithia-2,5-piperazinediones. Gliotoxin (2) exhibits potent antifungal, antiviral and bacteriostatic activities.<sup>14,15,16</sup> However, as with most other epidithia-2,5-piperazinediones, gliotoxin also displays high mammalian toxicity that has thus far precluded its therapeutic use. The pharmacological interest presumably lies in the hope that a suitable metabolite, derivative or

## Gliotoxins



2 R=H gliotoxin

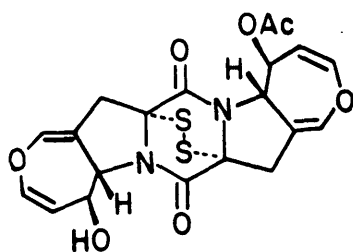
32 R=Ac gliotoxin acetate



33

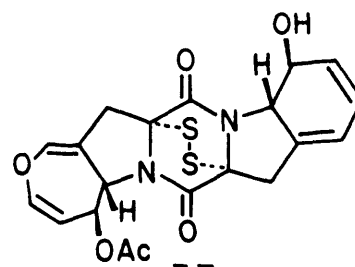
dehydrogliotoxin

## Aranotins



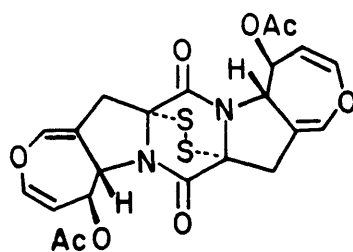
34

aranotin



37

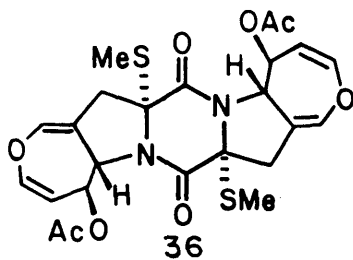
apoaranotin



35

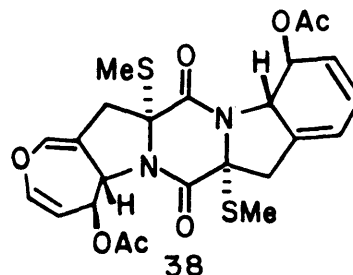
acetylaranotin

LL-S88a



36

bisdethio-di(methylthio)-acetylaranotin



38

bisdethio-di(methylthio)-apoaranotin

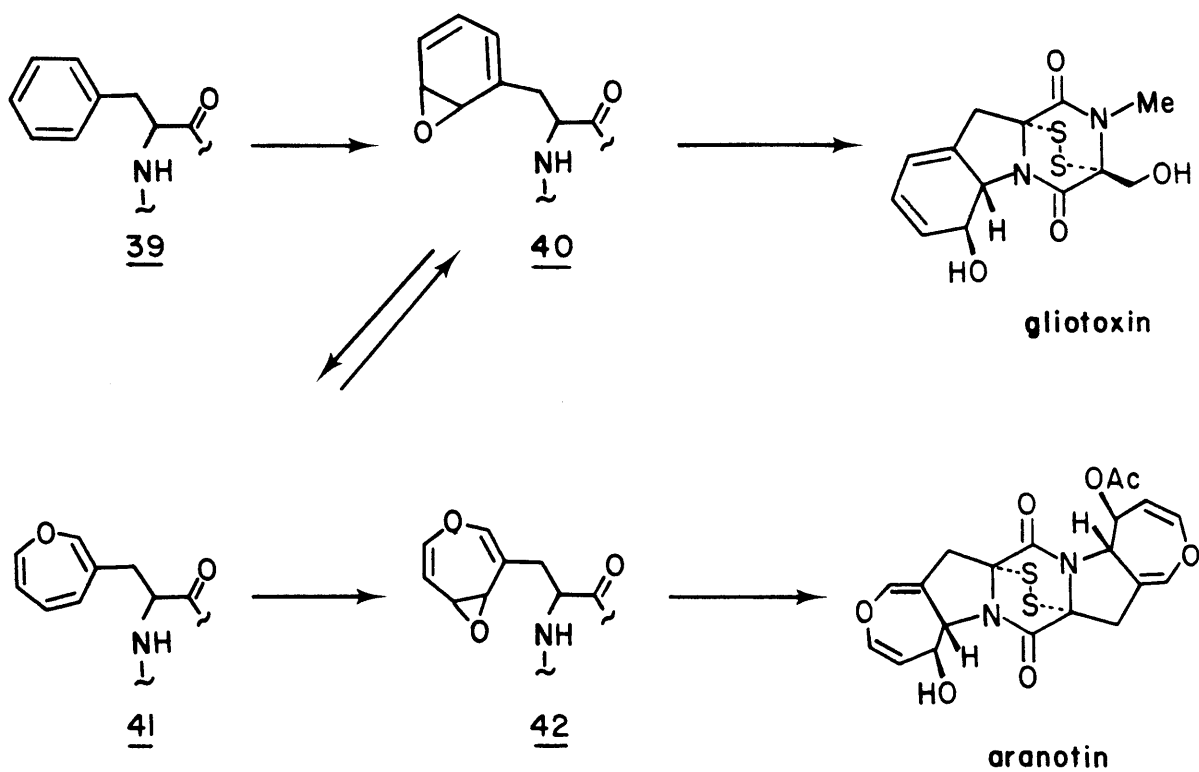
synthetic epidithia-2,5-piperazinedione will retain the antiviral, anti-tumor, etc. properties but not exhibit the mammalian toxicity. Such a compound has yet to be found amongst epidithia-2,5-piperazinediones.

The synthetic and biosynthetic interest in gliotoxin and the aranotins, aside from that discussed above, obviously lies in the fascinating structures this family of metabolites possesses.

Investigations by two groups<sup>17-22</sup> have shown that L-phenylalanine is incorporated efficiently into gliotoxin (2) and biosodethio-di(methylthio)-acetylaranotin (36) without rearrangement. In addition, the five aromatic protons of L-phenylalanine are all incorporated into gliotoxin. These results, as well as consideration of the similarity between the gliotoxin and aranotin structures led Neuss, et al<sup>25</sup> to propose the elegant sequence depicted in SCHEME 3. The intermediacy of an arene oxide (41) and oxepin oxide (43) is consistent with the labelling studies mentioned above, and the stereochemistry of the dihydroarene and dihydrooxepin moieties of the natural products.\* Recent work by Bu'Lock, Ryles, Johns and Kirby suggests that gliotoxin may originate from cyclization of a phenylalaine epoxide 41 or 44 (SCHEME 4); either isomer could give the correct stereochemistry.

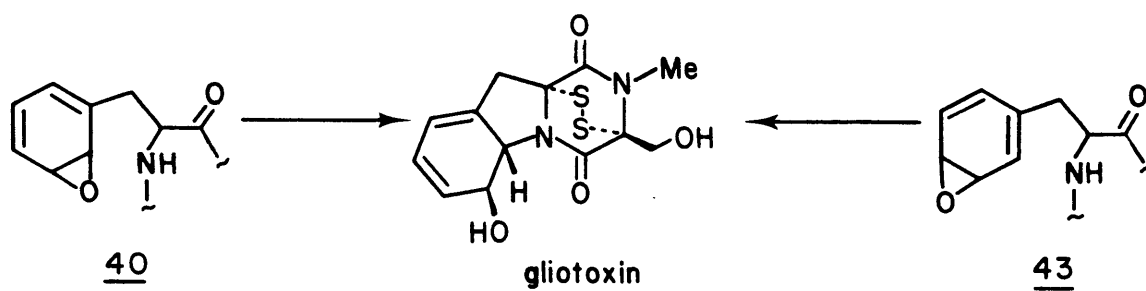
\* This scheme is also consistent with the "NIH shift" observed by Witkop in aromatic hydroxylations.

SCHEME 3 Neuss, et.al.

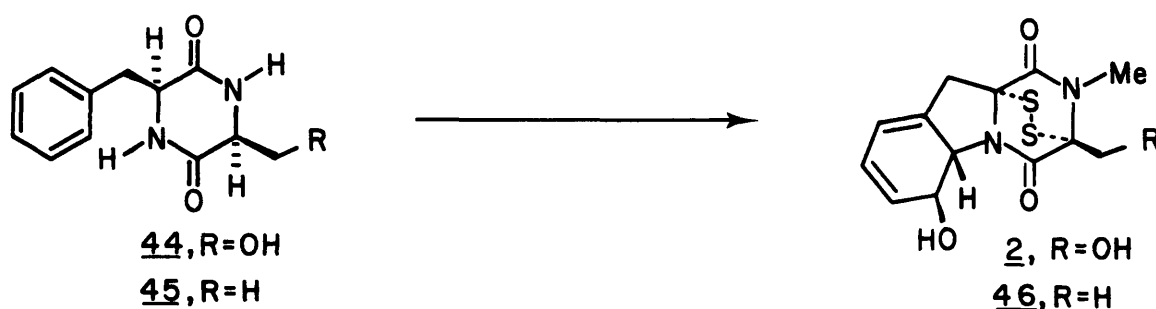


SCHEME 4

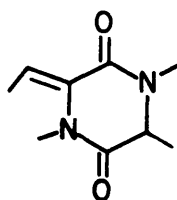
Bu'Lock, Ryles, Kirby and Johns



Feeding experiments by two groups<sup>23,24,26</sup> suggest that diketopiperazine formation precedes hydroxylation of the aromatic ring as well as incorporation of the sulfur atoms into gliotoxin (i.e., 44 → 2; 45 → 46)

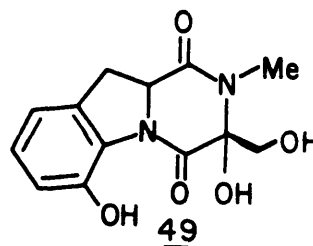
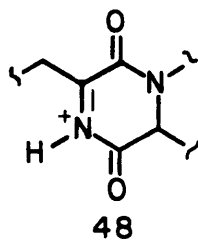


The problem of in vivo sulfur incorporation into these metabolites is not well understood. Labelling experiments<sup>27</sup> with phenylalanine  $d_8$  have shown that all five aromatic protons and both methylene protons are efficiently incorporated into acetylaranotin. This suggests that dehydrodipeptides (i.e., 47) are not involved during biosynthesis.

47



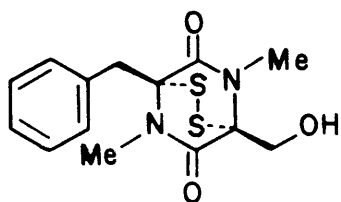
However, Sammes<sup>6b</sup> has suggested that intermediates such as 48 may trap



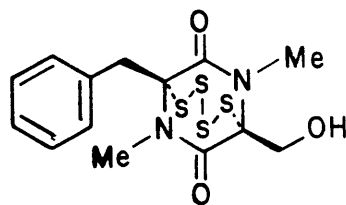
a sulfur nucleophile before loss of a proton and formation of a dehydrocyclodipeptide. Taylor<sup>6a</sup> suggested glycol structure 49 as a possible biosynthetic precursor to dehydrogliotoxin; the  $\alpha$ -hydroxy group presumably being replaced by a sulfur nucleophile. Whatever the intermediates may be, there seems to be general agreement that the diketopiperazine is formed early on, is then oxidized and trapped by some type of sulfur nucleophile. Variations on this idea have been tried in vitro, and will be discussed in more detail in the following section on synthetic studies.

The simplest family of naturally occurring epidithia-2,5-piperazinediones are the recently discovered hyalodendrins (50-56). It is interesting that both antipodes have been discovered, and were shown to display different physiological activities. Strunz<sup>28,31</sup> has shown that hyalodendrin (53) (3S,6S) displays antifungal activity against a variety of microorganisms and is comparable to benomyl in its ability

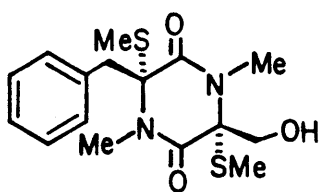
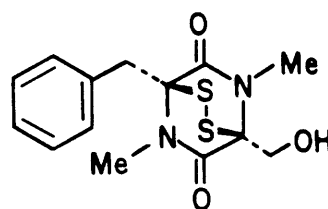
# Hyalodendrins



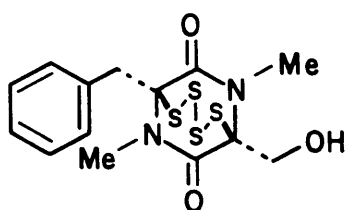
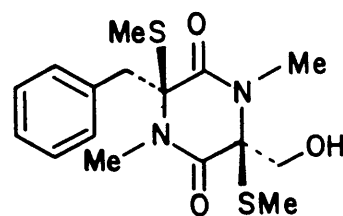
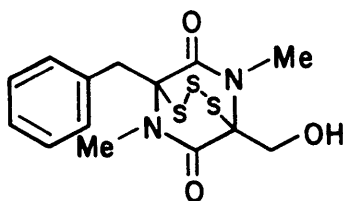
A26771A

50

A26771C

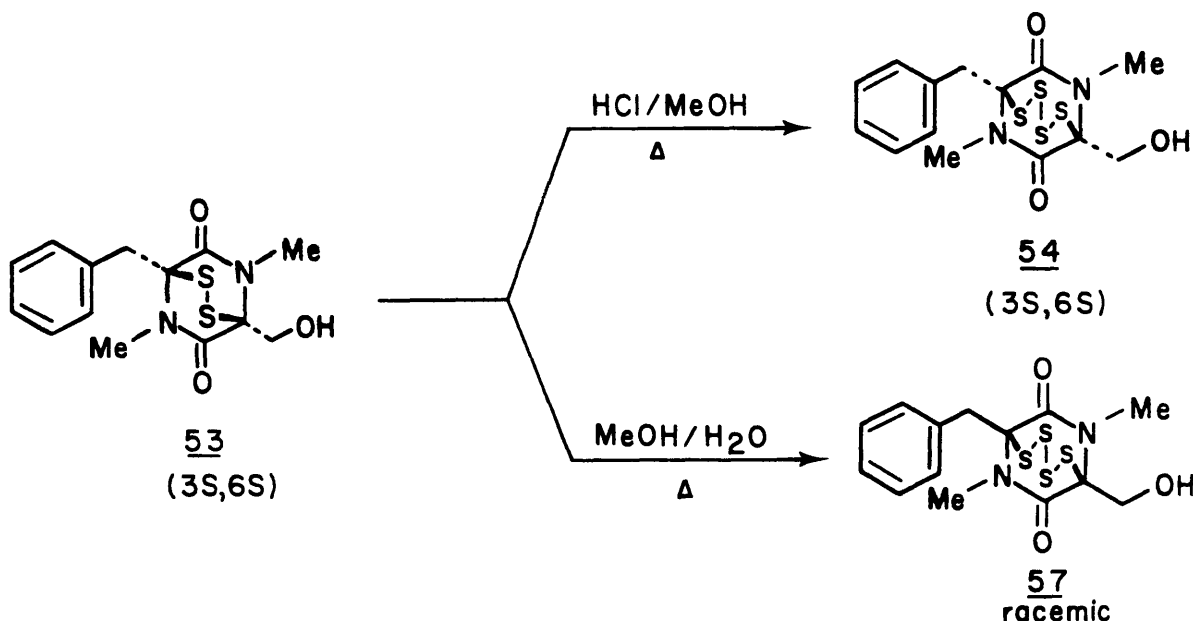
51A26771E  
GLIOVICTIN52

HYALODENDRIN

53545556

to inhibit Ceratocystis ulmi, the causal agent of Dutch Elm disease. Hyalodendrin is produced by a species of Hyalodendron sp.; a contaminant isolated from a plate culture.<sup>36</sup> The Lilly group reported<sup>33</sup> the fermentation, isolation, antiviral properties and X-ray of the antipodal (3R, 6R configuration) series. These metabolites (50-52) were produced from cultures of Penicillium turbatum, obtained from a soil found on Mt. Arat in Eastern Turkey. DeVault and Rosenbrook<sup>35</sup> obtained the disulfide, trisulfide (56) and bis-dethio(methyl-thio) compounds of undetermined absolute configuration, from an unidentified, sterile fungus.

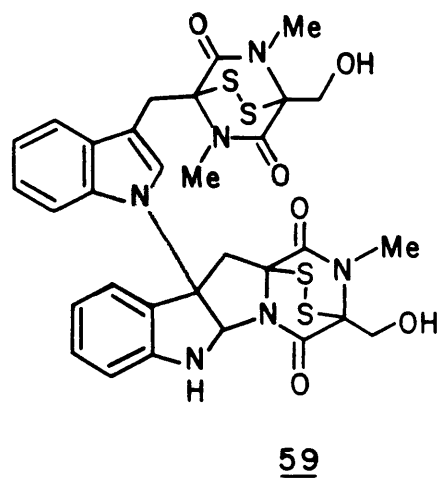
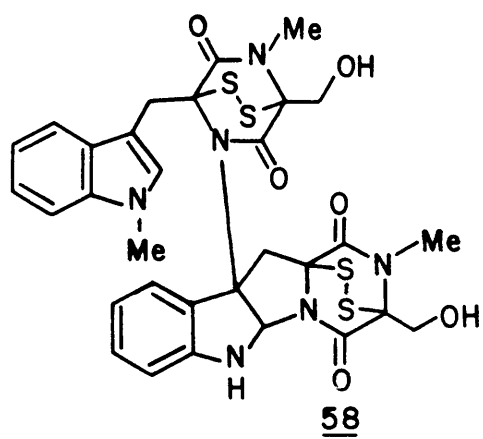
An unusual transformation of hyalodendrin into the corresponding tetrasulfide was reported by Strunz;<sup>30</sup> refluxing hyalodendrin (53) in methanolic HCl produced a modest yield of tetrasulfide (54) with 3s, 6s configuration. However, refluxing hyalodendrin in aqueous methanol solution without addition of HCl led to the production of racemic tetrasulfide (57) in good yield.



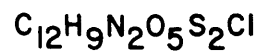
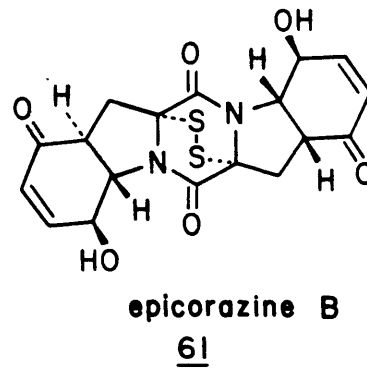
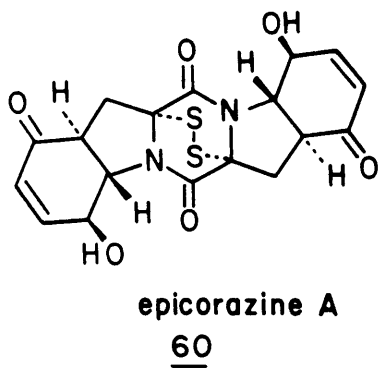
Chetomin was isolated over 30 years ago by Waksman and Bugie<sup>37</sup> from a strain of Chaetomium cochliodes which is thought to be associated with poor growth in young ruminants. A tentative structure (58) for this metabolite was proposed by Safe and Taylor;<sup>38</sup> chetomin is an amorphous, glass-like solid and thus precluded an X-ray analysis. The correct structure for chetomin is now thought to be 59, and was deduced<sup>39,40</sup> with the aid of <sup>15</sup>N labeling, and <sup>15</sup>N and <sup>13</sup>C NMR spectroscopy. Since chetomin exhibits antiviral activity, it will be interesting to discover if the absolute configuration is of the expected gliotoxin type.

A recent addition to the epidithia-2,5-piperazinedione class of antibiotics is epicorazine A and B (60,61).<sup>41-44</sup> These metabolites were isolated from a strain of the fungus Epicoccum nigrum and show antibacterial properties. The two metabolites differ only in the chirality of a single asymmetric center. Deffieux, et al, do not consider this to be the result of epimerization during the isolation procedure.<sup>43</sup> It is also of interest that Epicoccum nigrum also produces 3,6-dibenzyl-2,5-piperazinedione (cyclo-L-phenylalanine).<sup>4</sup> No further biosynthetic correlations were, however, reported.

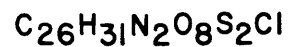
Two other metabolites which appear to contain the epidithia-2,5-piperazinedione moiety are A30641<sup>45</sup> (62) and oryzachlorin<sup>46</sup> (63). The detailed structures of these metabolites await full elucidation.



chetomin



**A30641**  
**62**

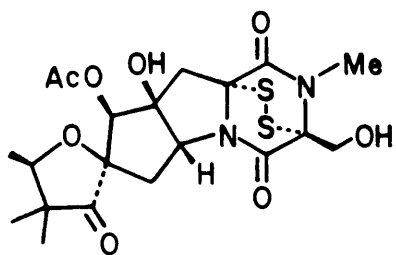


**oryzachlorin**  
**63**

The most recent addition to the gliotoxin-sporidesmin class of metabolites are the sirodesmins (64-67).<sup>47,48</sup> These metabolites have been shown to exhibit antiviral, phytotoxic and mycotoxic properties. Hesp, et al,<sup>47</sup> proposed an interesting biosynthetic sequence (SCHEME 5) reminiscent of the Neuss proposal (cf. SCHEME 3). Epimerization of 69 via the derived enol equivalent accounts for the stereochemistry present in sirodesmin A (64) and sirodesmin G (67).

The intermediacy of substituted  $\beta$ -aminoethyl benzene oxides (i.e. 40,43 and 68) in the biogenesis of gliotoxin and sirodesmin have been the subject of model studies in these laboratories.<sup>49</sup> The systems studied aromatized faster than cyclization could take place; such arene oxides were deemed to be of "low nucleophilic susceptibility".

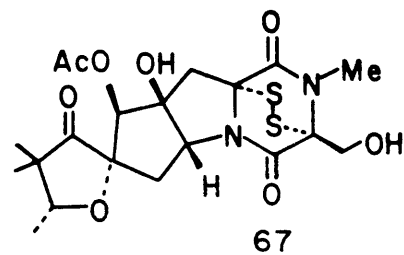
## Sirodesmins



sirodesmin A 64

trisulfide = sirodesmin B 65

tetrasulfide = sirodesmin C 66

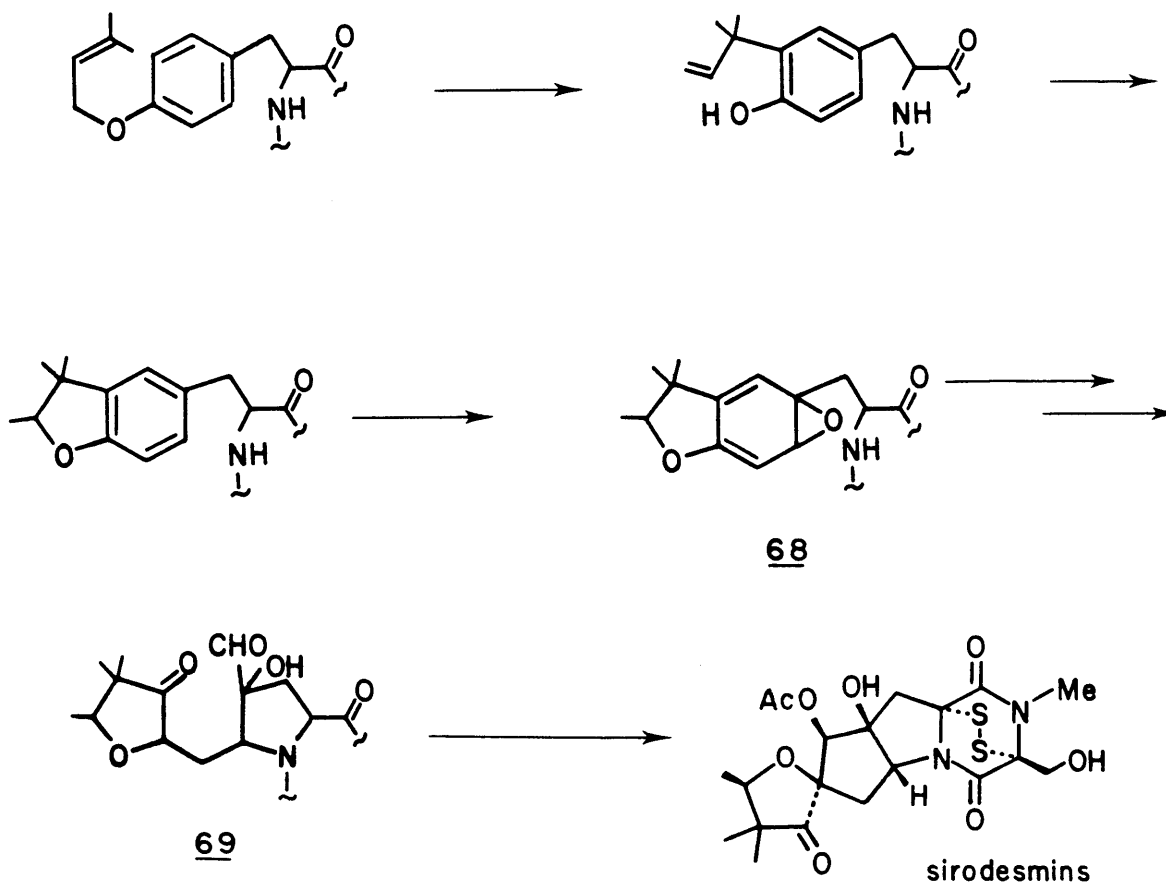


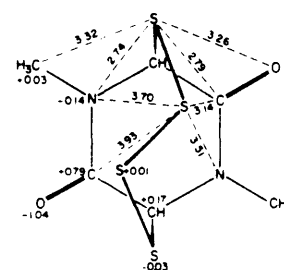
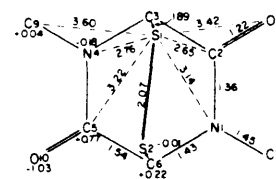
sirodesmin G 67

sirodesmin PL

### SCHEME 5

Biosynthesis of SIRODESMIN Hesp, et.al.





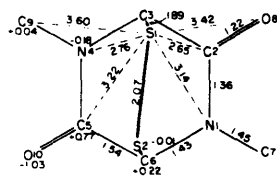
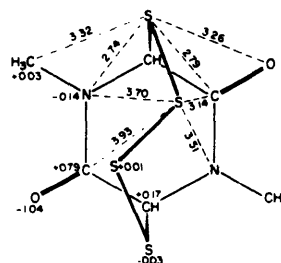
# Physical Properties &

## Characteristic Chemistry of

### Epipolythiapiperazinediones



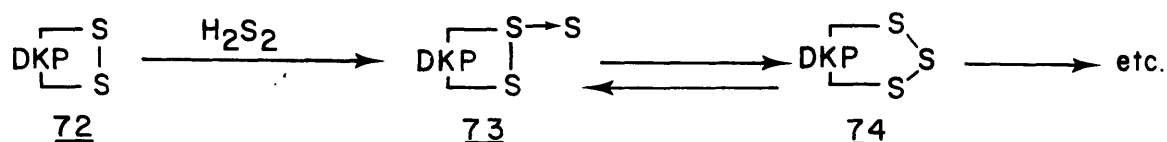
Acyclic disulfides generally adopt a dihedral angle of 74-105° about the C-S-S-C- group and the S-S bond length is generally 2.03-2.05Å.<sup>6c,51</sup> X-ray analyses<sup>6c,50,51</sup> of several naturally occurring epidithia-2,5-piperazinediones have revealed that the strained disulfide bridge in these metabolites has dihedral angles ranging from 8° (chaetocin) to 18° (acetylaranotin). The S-S bond lengths were also found to be longer (2.068-2.082Å). In addition, these studies have revealed that the helicity of the disulfide bond is such that each sulfur atom is spatially closer to the adjacent carbonyl carbon atom rather than to the adjacent nitrogen atom (i.e., 70). Hence, the stereochemistry of the epidithia-2,5-piperazinedione system involves not only the chirality of the nonamide carbon atoms, but also the more unusual asymmetry provided by the helix of the disulfide. In contrast, Przyblska and Gregory<sup>50</sup> have found that epitetrathio-2,5-piperazinediones are skewed in such a way so that the inner sulfurs are closer to the nitrogens and the outer sulfurs are closer to the carbonyl carbons (i.e., 71)

7071

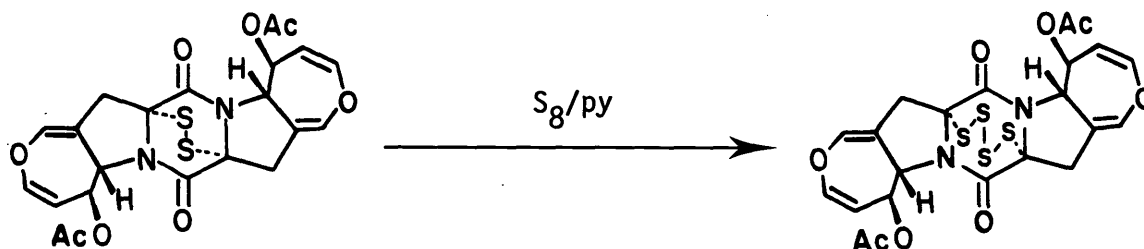
The strain of the disulfide bridge is reflected by the ease with which they are opened; reduction with sodium borohydride proceeds rapidly at 0°C. It was at first surprising to discover<sup>6a</sup> that the corresponding dithiols are easily oxidized back to the disulfides by a variety of mild oxidizing agents (i.e., air, ethyl iodide, DDQ, KI<sub>3</sub>/PY, Ellman's reagent, etc.). Indeed, Whitesides<sup>52</sup> has found that 3,6-dimercaptopropylproline anhydride (106) is comparable in reducing ability towards disulfides to dithiothreitol.

#### Characteristic Reactions<sup>6a-c</sup>

As was noted earlier, the disulfide bridge can be cleanly reduced with sodium borohydride, or by thiol-disulfide exchange with mercaptans. The resulting 3,6-dimercapto-2,5-piperazine-diones can be converted into the epitriethia and epitetrathia derivatives by reaction with sulfur dichloride and sulfur monochloride, respectively. The dimercaptans can also be alkylated; e.g., with methyl iodide in pyridine to afford the naturally occurring bis dethio(methylthio) derivatives. In addition, the disulfides (72) react with dihydrogen disulfide to form the epitriethia (74) and epitetrathio derivatives. This reaction is thought to involve branched sulfur chains (i.e., 72 + 73).



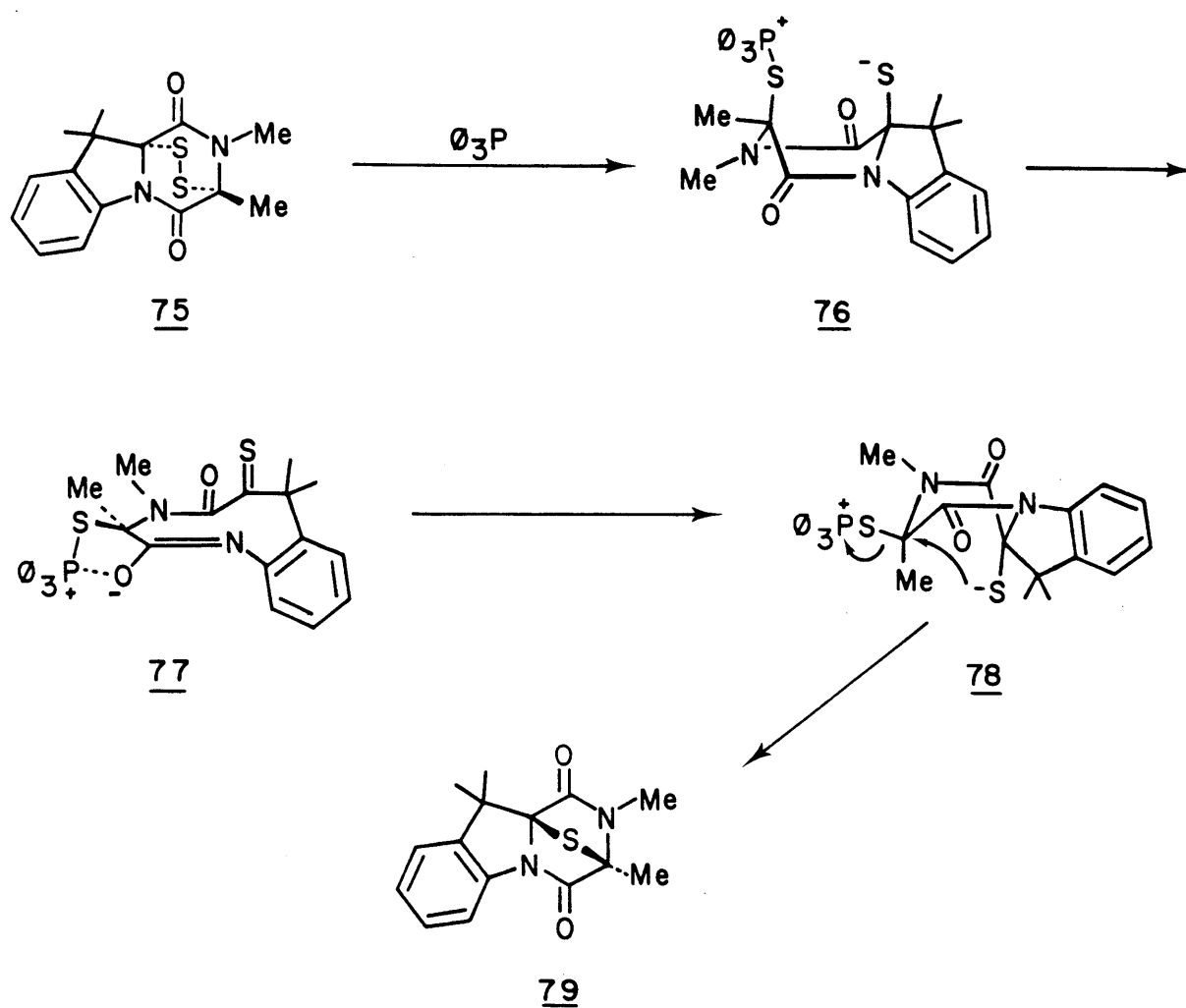
DKP= diketopiperazine



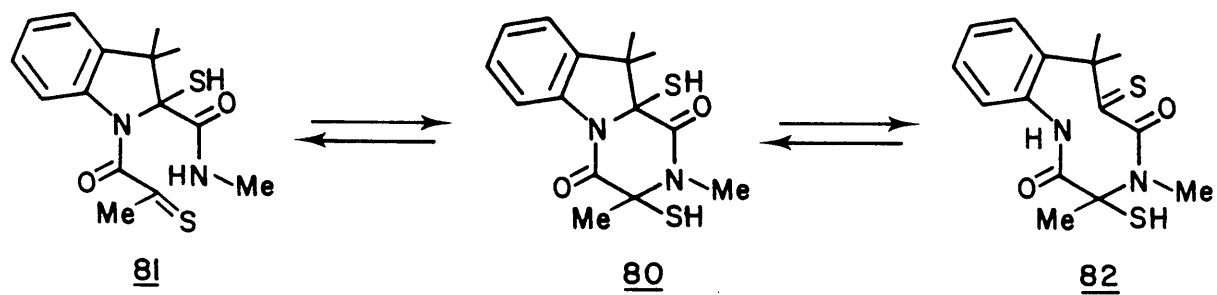
Murdock<sup>109</sup> has also found that reaction of acetylaranotin with 2 equiv. of elemental sulfur in pyridine produces 81% of acetylaranotin tetrasulfide. Taylor<sup>69</sup> has speculated that the above sulfur-insertion reactions may be operating in vivo, thus accounting for the occurrence of the natural epitritia and epitetrathiapiperazinediones.

One of the most interesting reactions of the epidithia-2,5-piperazinedione moiety is the desulfurization with phosphines. Thus, dehydrogliotoxin,<sup>9g</sup> sporidesmin<sup>9g</sup> and sirodesmin<sup>48</sup> have been shown to give the corresponding epimonosulfides upon reaction with triphenylphosphine. On the basis of CD studies, Safe and Taylor<sup>9g</sup> proposed that this reaction proceeds with net inversion of configuration at both bridgehead carbon atoms. This was suggested because the CD curves of the starting epidithia-

SCHEME 6 Ottenheijm, et.al.



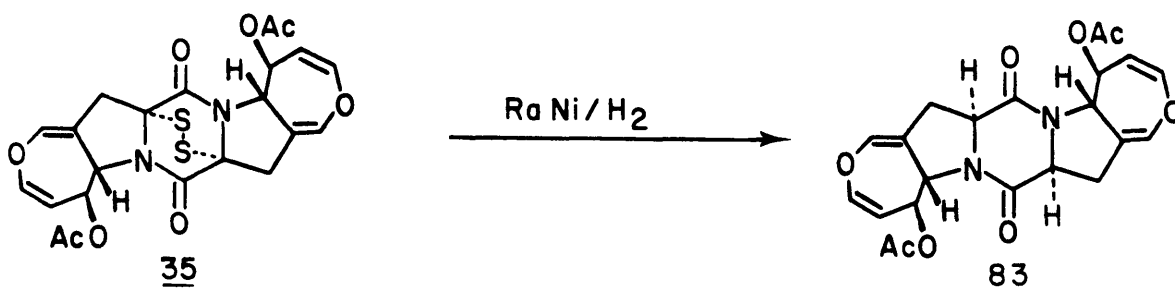
SCHEME 7



2,5-piperazinediones and product epimonosulfides showed opposite signs. Sammes<sup>6b</sup> regarded this interpretation as "mechanistically unfeasible", arguing that an interaction of chromophores in the disulfide may be absent in the monosulfide, thus discrediting comparison of the CD curves. Ottenheijm and co-workers<sup>53</sup> have recently demonstrated that desulfurization of their synthetic gliotoxin analog (75) with triphenylphosphine does indeed proceed with inversion of configuration. The stereochemical course of their reaction was confirmed by X-ray analysis, NMR spectroscopy in the presence of a chiral shift reagent and comparison of CD curves. A mechanism was proposed<sup>53</sup> for this reaction (SCHEME 6) and is thought to involve regiospecific attack of the phosphine on the least hindered sulfur (76). Ring opening via thiocarbonyl compound 77, followed by conformational flip of 77 and ring reclosure affords 78 which suffers S<sub>N</sub>2 type displacement of triphenylphosphine sulfide to give enantiomeric epimonosulfide (79). Ottenheijm has suggested<sup>53</sup> that dithiols (i.e., 80) may also be in equilibrium with their thiocarbonyl tautomers (i.e., 81, 82). A similar epimerization mechanism involving a thiocarbonyl intermediate was also proposed by Leigh and Taylor,<sup>6c</sup> and Kishi.<sup>54</sup>

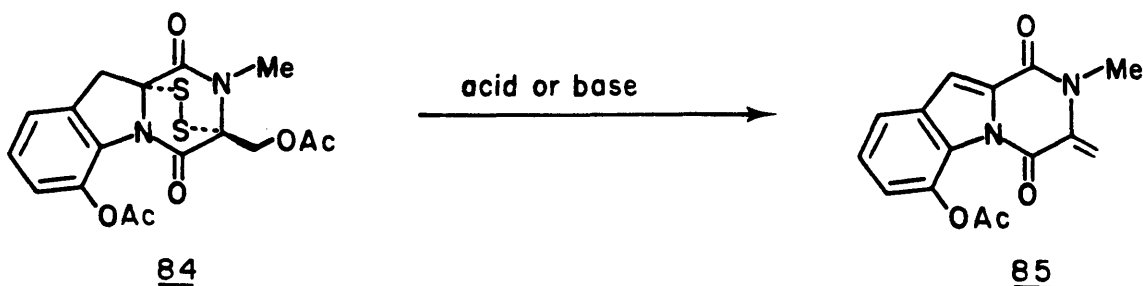
The chiroptical studies of Ottenheijm,<sup>53</sup> Herrmann,<sup>9m</sup> Nagarajan<sup>57</sup> and others<sup>6c</sup> demonstrate that the CD curves of epipolythia-2,5-piperazinediones are highly characteristic of this moiety and allow the natural products that have been isolated to be classified into two enantiomeric groups.

Complete removal of sulfur from these metabolites can be achieved in a number of ways.<sup>6a-c</sup> Reaction with Raney nickel or aluminum amalgam affords, in most cases, the dethio compounds. Reaction of acetylaranotin (35) with Raney nickel afforded the dethio compound (83) with retention of configuration at the asymmetric centers.



Retention of configuration in these reductive sulfur eliminations is not general and varies from one family of metabolites when compared to another. Thus, aluminum amalgam reduction of gliotoxin<sup>56</sup> appears to proceed with retention of configuration; similar reduction of hyalodendrin<sup>28</sup> gave a product with  $[\alpha]_D = 0^\circ$ .

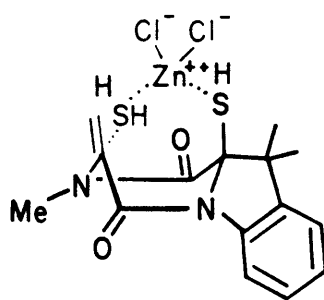
The sulfur function may also be eliminated under anhydrous acidic or basic conditions.<sup>6a,c</sup> The reaction proceeds best when the metabolite contains a hydroxymethyl or methinoxy substituent which is esterified (i.e., 84  $\rightarrow$  85).



Safe and Taylor<sup>9h</sup> found best results when the metabolite is simply refluxed in dry pyridine. This type of desulfurization has been useful for structure elucidation, since all the known varieties of these metabolites undergo the reaction and one can often obtain a single, easy to identify diene from a complex mixture of metabolites.

Epidithia-2,5-piperazineiones also lose the  $[S_2]$  fragment in the mass spectrometer; the resulting  $(M^+ - S_2)$  ion generally being abundant.

## Synthetic Studies

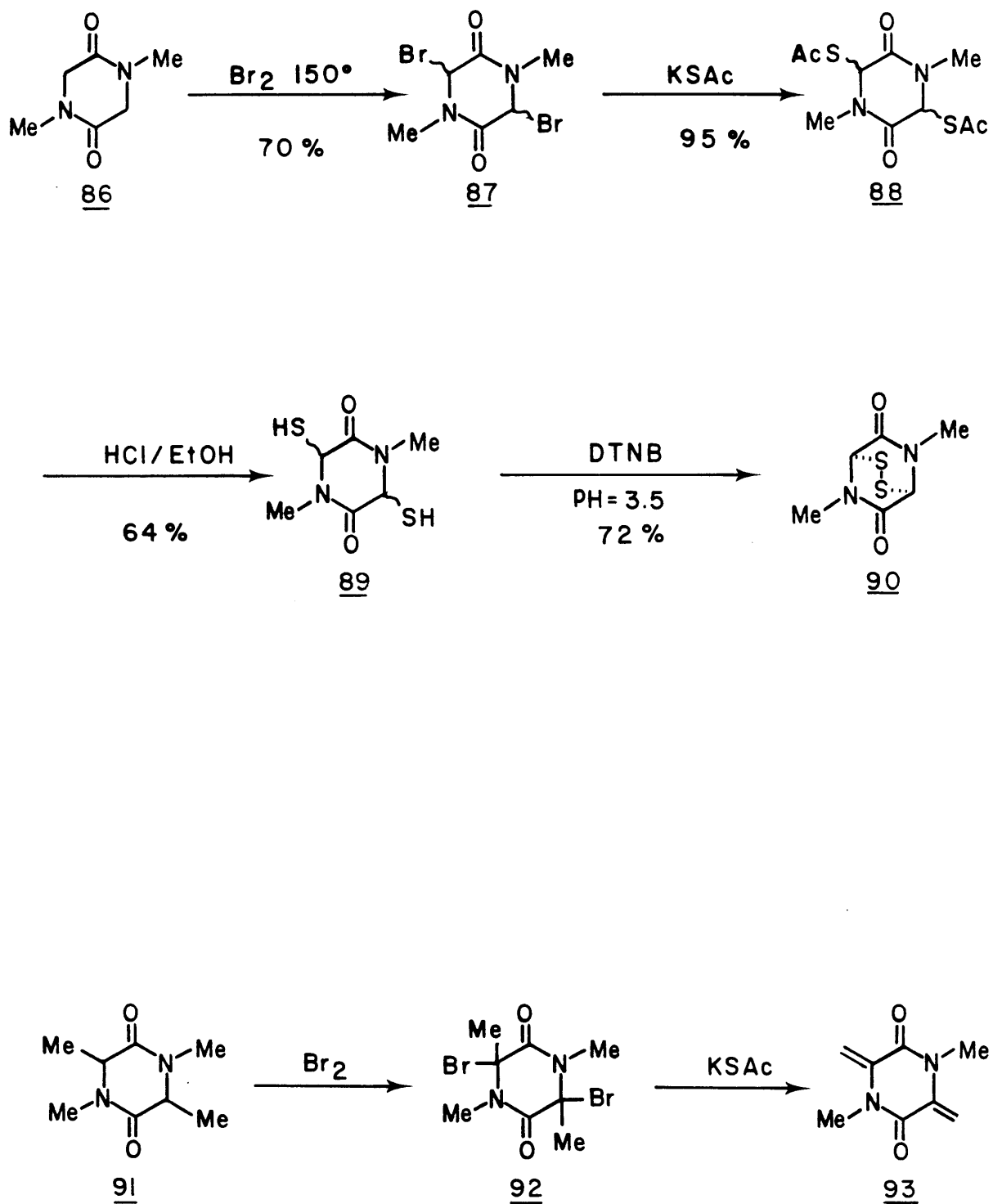




The general biological activity of epidithia-2,5-piperazinediones as well as the synthetic challenge posed by their complex and delicate structures have stimulated a great deal of synthetic activity over the past ten years. The first synthesis of an epidithia-2,5-piperazinedione was that achieved by Trown<sup>58</sup> in 1968 (SCHEME 8). Bromination of the readily available 1,4-dimethyl-2,5-piperazinedione (sarcosine anhydride) 86 in o-dichlorobenzene at 150° afforded the crystalline 3,6-dibromide 87, in 70% yield. Nucleophilic displacement of the bromine atoms with potassium thiolacetate afforded the corresponding 3,6-dithioacetate (88) in 95% yield. Hydrolysis of 88 in ethanolic HCl gave the dithiol 89 (64%) which was oxidized to the disulfide (90) with Ellman's reagent in 72% yield. Disulfide 90 exhibited potent antiviral activity and was thus compelling chemical evidence that the active fragment of these fungal metabolites is the epidithia-2,5-piperazinedione moiety. Synthesis of dithiols such as 89 by the Trown approach has been exploited by others<sup>6a-c</sup> and is the cornerstone of Kishi's total syntheses of sporidesmins A and B, dehydrogliotoxin, gliotixin and hyalodendrin; these will be discussed at the end of this section.

Several problems are present in the synthetic approach of Trown. When the bromination reaction was extended to substituted piperazinediones (i.e., 91 → 92) unfavorable dehydrobromination takes place,<sup>59,60</sup> forming olefins (93). A partial solution to this problem was reported by Yoshimura,

SCHEME 8 P.W. Trown

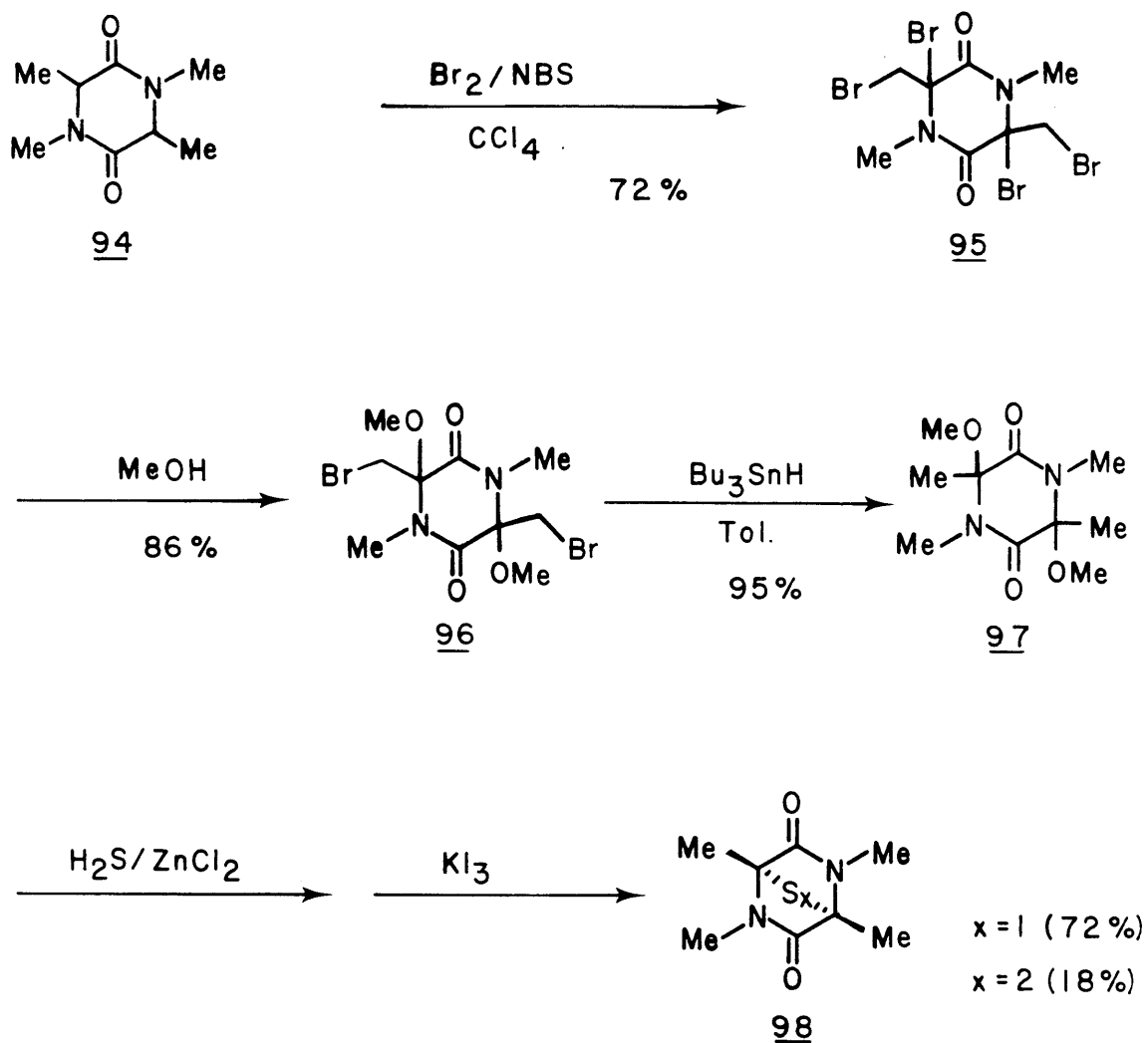


et al<sup>61</sup> and is illustrated in SCHEME 9. Tetrabromide 95 was prepared by bromination of 1,3,4,6-tetramethyl-2,5-piperazinedione 94. Methanolysis afforded 96 which was reduced with tri-n-butyltinhydride in toluene to afford 97. Successive treatment of 97 with H<sub>2</sub>S in the presence of ZnCl<sub>2</sub> followed by KI<sub>3</sub> oxidation produced a mixture of epidithia and epimonothia compounds (98).

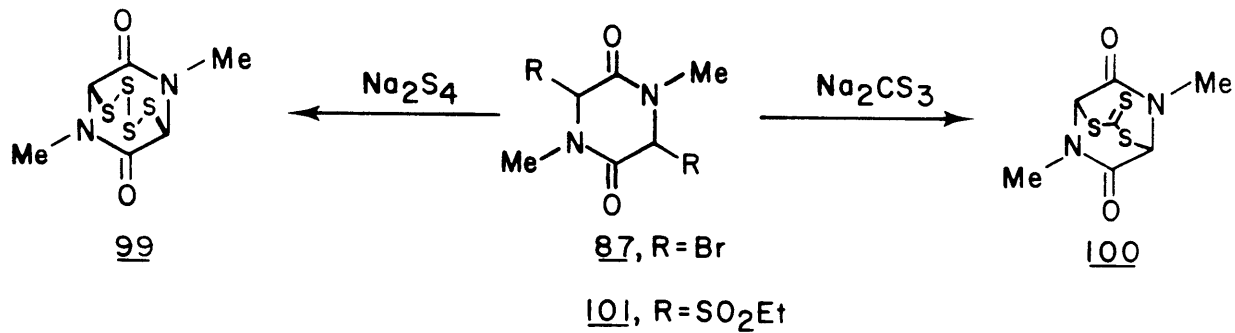
Another drawback of the Trown approach is that introduction of the bromines and subsequent thiol functionalities proceeds in a nonstereospecific manner, giving a mixture of cis and trans dimercaptans. Schmidt and co-workers<sup>62,63</sup> developed a clever way of (conceptually) circumventing this stereochemical problem (SCHEME 10). Reaction of dibromide 87 with bifunctional sulfur nucleophiles such as sodium tetrasulfide or sodium trithiocarbonate affords the corresponding epitetrasulfide 99 (67%) and epitritthiocarbonate 100 (48%). The displacement reaction with sodium tetrasulfide on the bis-ethylsulfone (101) has also been reported.<sup>64</sup>

In a series of extensive studies, Schmidt<sup>64-69</sup> and co-workers introduced both nucleophilic and electrophilic sources of sulfur into L-prolyl-L-proline anhydride (102). Lead tetraacetate oxidation<sup>69</sup> of 102 afforded the diacetoxo derivative 104, which upon hydrolysis gave the cis-diol 105. Replacement of the hydroxy groups with hydrogen sulfide in the presence of zinc chloride afforded cis-dimercaptan 106 which was smoothly oxidized to the epidithiaprolyl proline

## SCHEME 9



## SCHEME 10



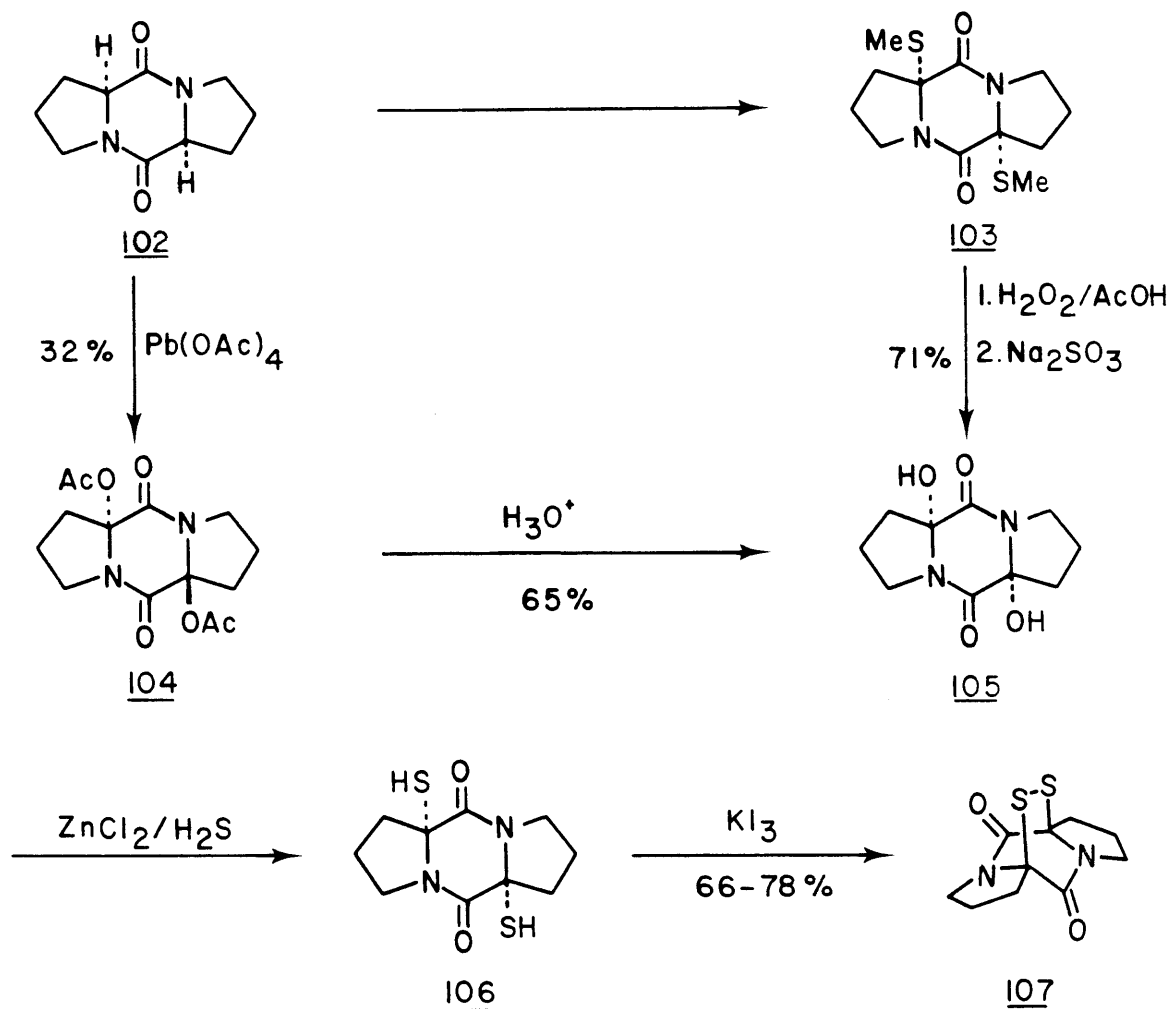
anhydride 107. Diol 105 was also obtained<sup>68</sup> from bis-methylthio compound 103; oxidation with hydrogen peroxide produced an intermediate bis-peroxide which was reduced with sodium sulfite to 105.

In an alternate approach, Schmidt and co-workers<sup>65,66</sup> sequentially metallated and sulfenylated 102 with sodium amide in liquid ammonia and elemental sulfur (SCHEME 12). Thus, crude mercaptide 108 was treated with another equivalent of base and sulfur to form bis-oligosulfide 109. Reduction of 109 with sodium borohydride gave dimercaptan 106 which was oxidized with  $\text{KI}_3$  in  $\text{H}_2\text{O}/\text{CHCl}_3$  to afford epidithia-L-poly-L-proline anhydride. The product so obtained retained the absolute configuration of the optically active starting material (102).

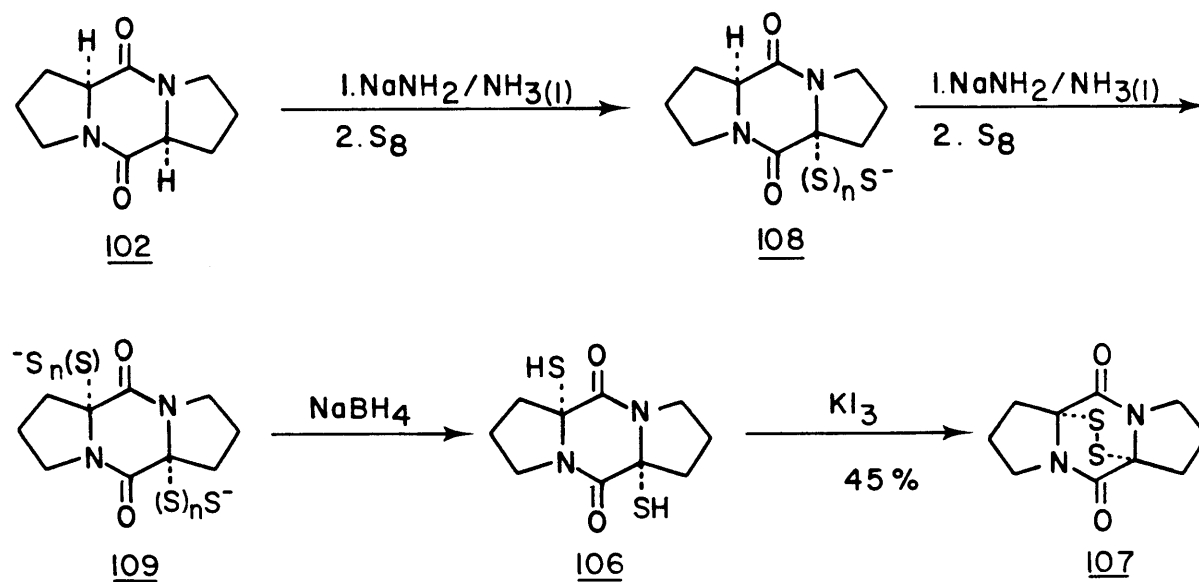
More recently, Schmidt and co-workers<sup>70,71</sup> applied a modification of their earlier approach (cf. SCHEME 11 and SCHEME 13) to the construction of the disulfide bridge in alanylproline anhydride (113).

Using essentially the same method, Ottenheijm and co-workers<sup>72-74</sup> reported on the synthesis of a gliotoxin analog (75) via zinc chloride catalyzed addition of  $\text{H}_2\text{S}$  across thio-olefin 118. The cis orientation of mercaptan groups in 120 is thought to be the result of zinc directed sulfenylation (i.e., 119).<sup>79</sup>

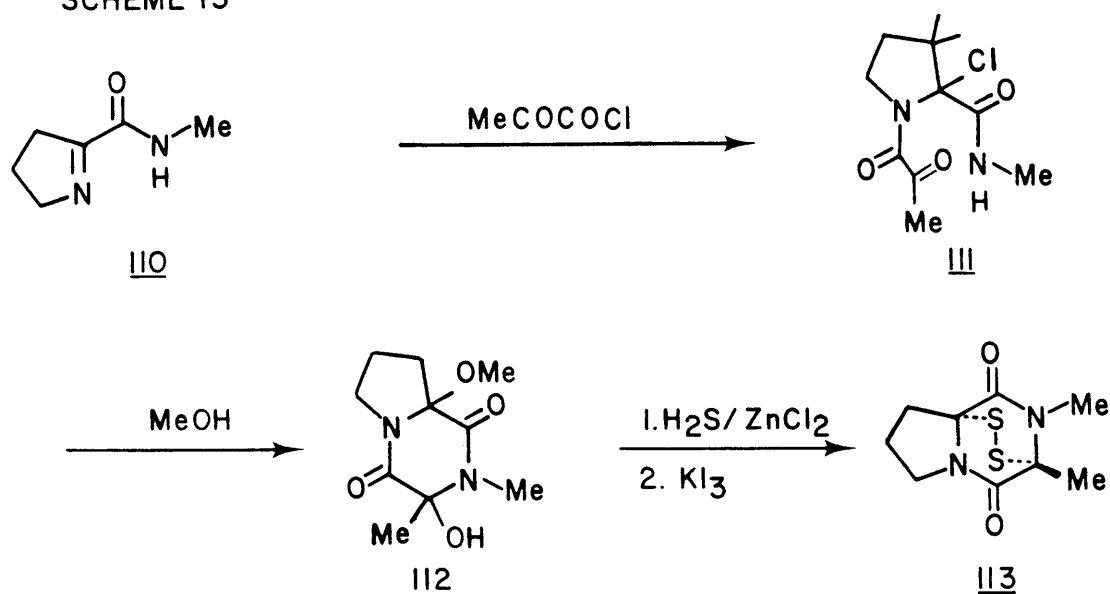
## SCHEME 11



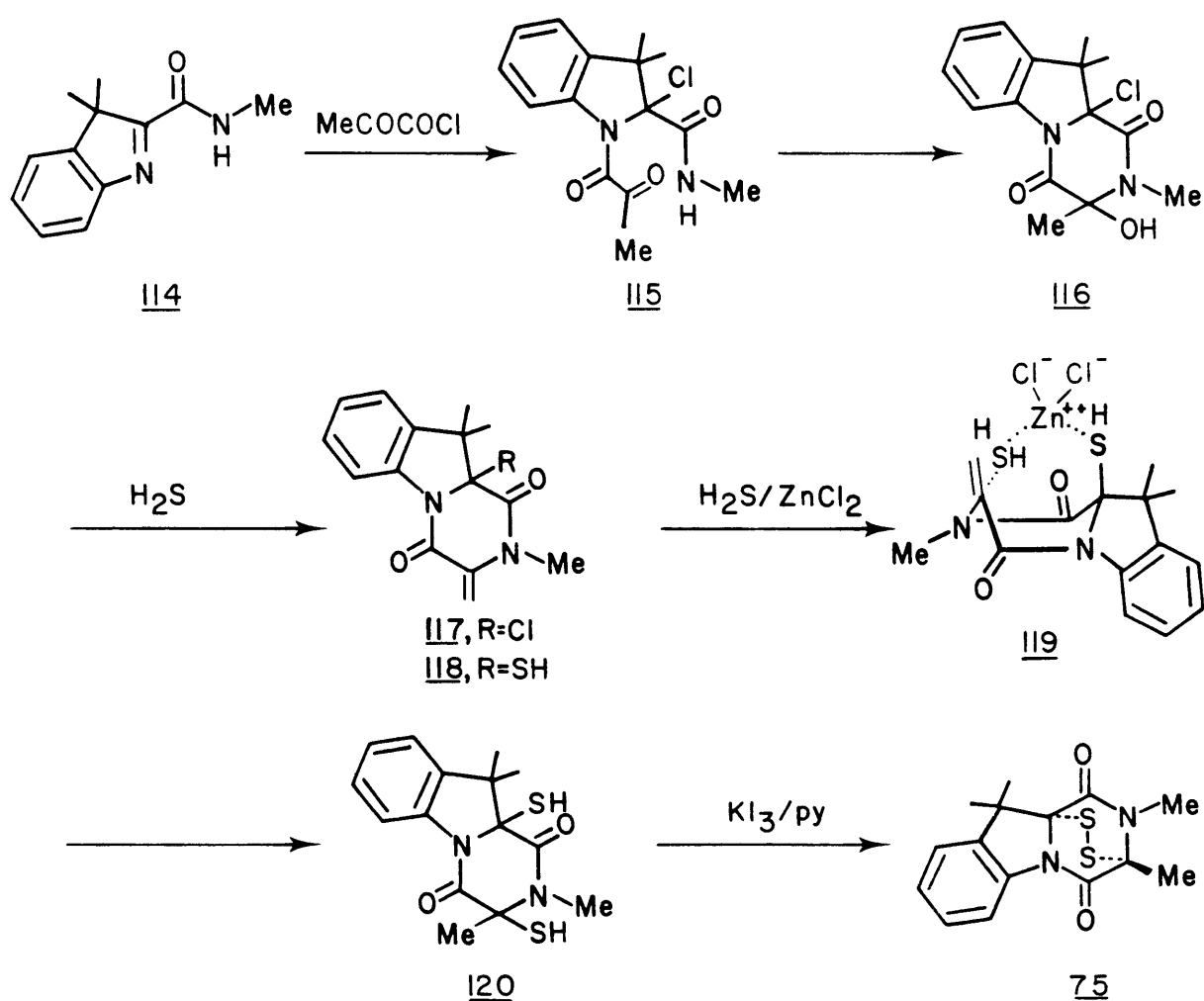
## SCHEME 12



SCHEME 13



SCHEME 14



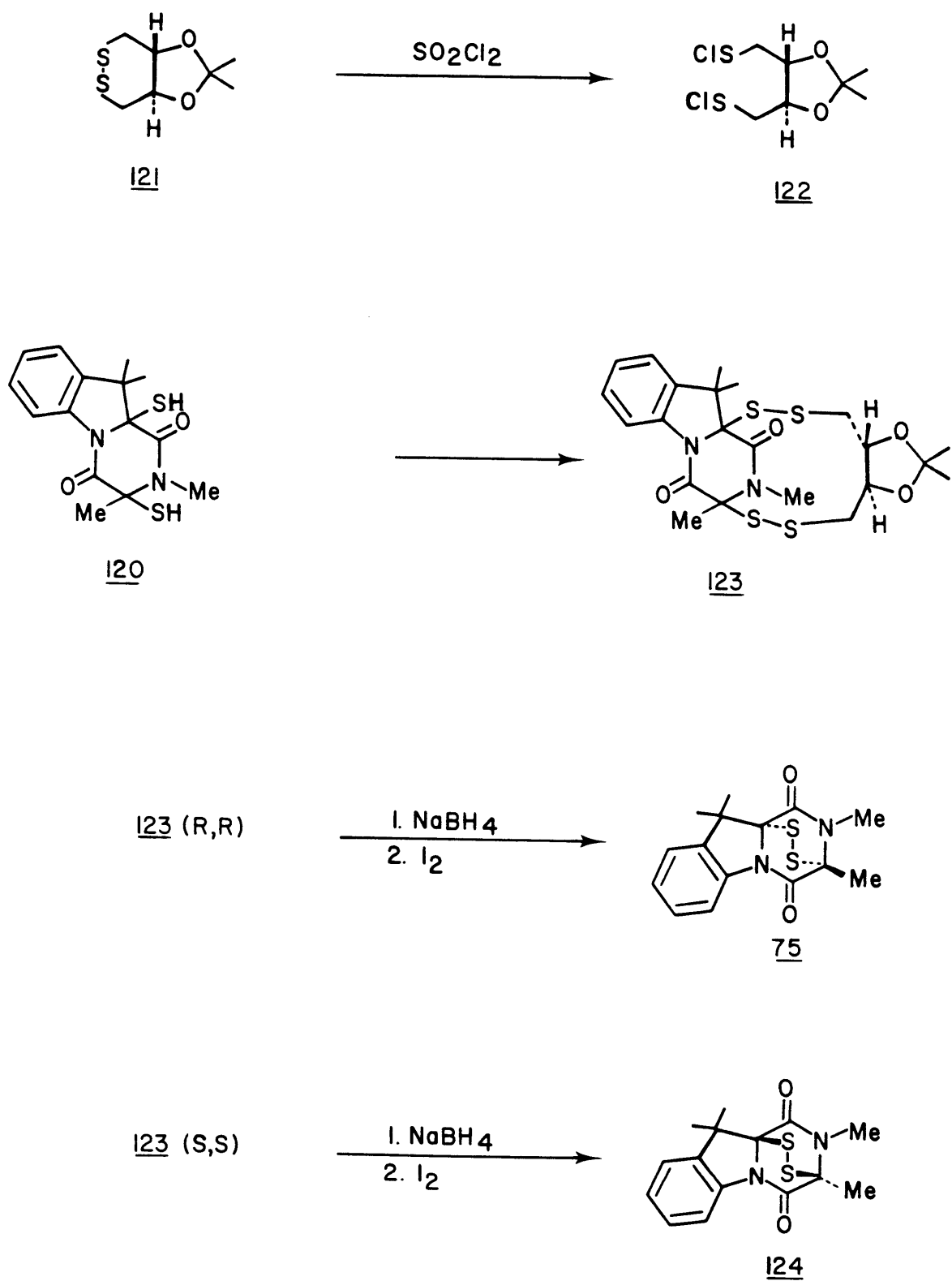
The similarities of Ottenheim's and Schmidt's syntheses have resulted in some (amusing) disagreement between the respective parties about scientific originality and proper accreditation. Schmidt recently published<sup>75</sup> a scathing "Bemerkungen zur 'Three-step Synthesis of a Gliotoxin Analogue....' von H. C. J. Ottenheim, et al.." Ottenheim rapidly replied,<sup>76</sup> citing his earlier work,<sup>77,78</sup> etc.

During the course of Ottenheim's synthetic<sup>72-74</sup> and chiroptical<sup>53</sup> studies, a method for the chemical resolution of epidithia-2,5-piperazinediones was reported<sup>7</sup> (SCHEME 15). Thus, chromatographically separable diastereomers (i.e., 123) were obtained by reaction of the dithiol derived from the epidithia-2,5-piperazinedione (i.e., 120) with the disulphenyl chloride (122) derived from isopropylidene dithiothreitol (121). From these, the optically pure enantiomers 75 and 124 were obtained by reduction with sodium borohydride followed by reoxidation with I<sub>2</sub> in pyridine. Interestingly, both enantiomers exhibited similar antiviral activities, indicating that previous<sup>6a-c</sup> configuration-activity notions may be incorrect.

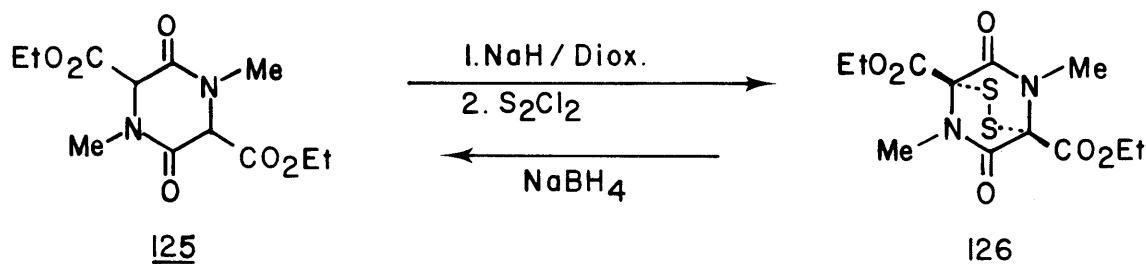
An interesting method for introduction of the disulfide functionality into activated piperazinedione 125 has been developed by Hino and Sato.<sup>80,81</sup> Treatment of 125 with 2 equiv. of strong base affords the corresponding dianion which is quenched with S<sub>2</sub>Cl<sub>2</sub> to give a modest yield of epidithia-2,5-piperazinedione 126. An unusual desulfurization



## SCHEME 15



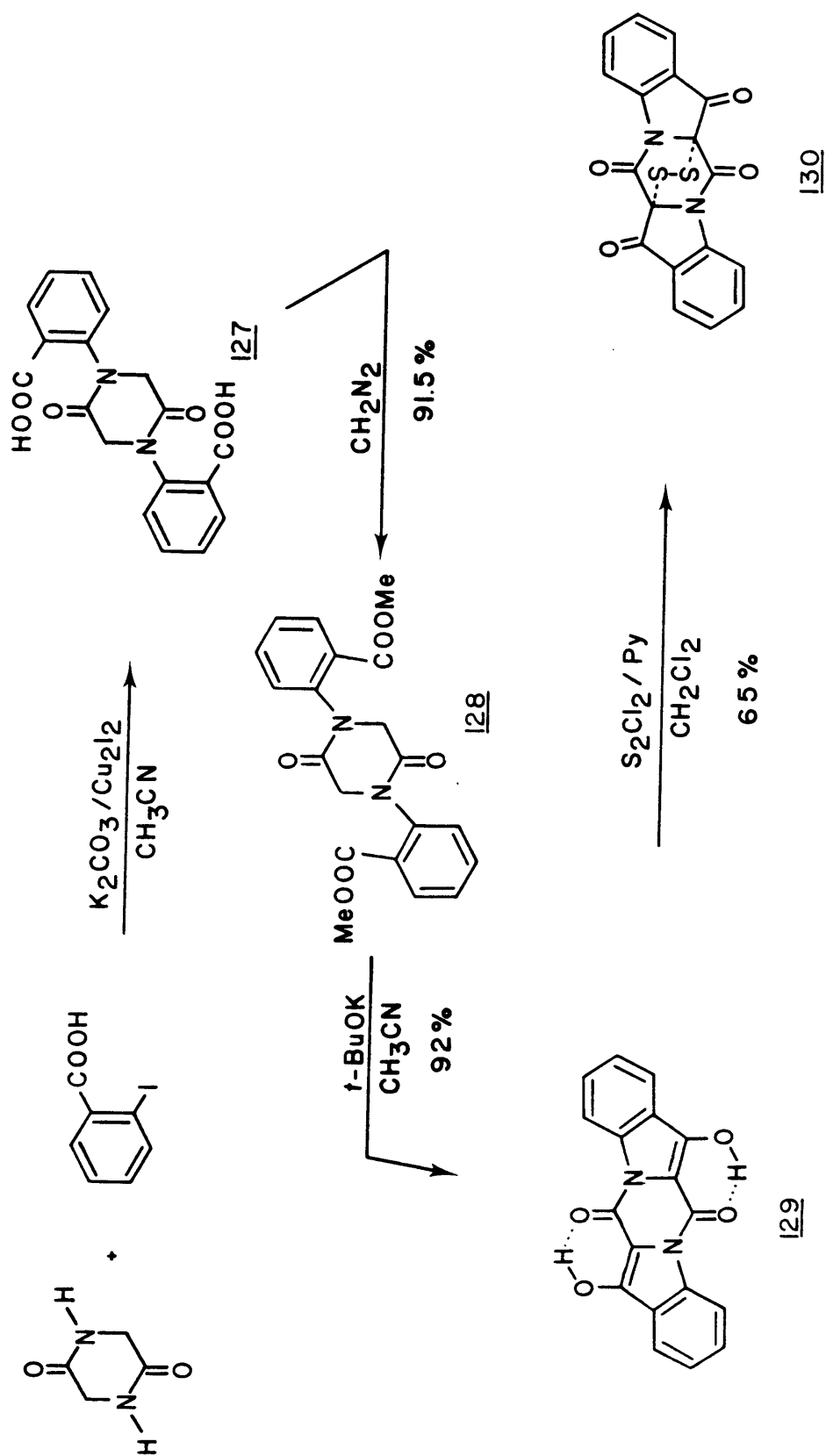
of 126 took place upon treatment with sodium borohydride. Starting material (125) was obtained rather than the expected dimercaptan.



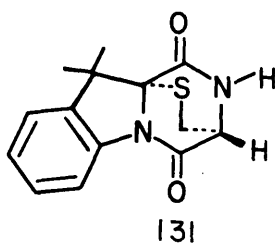
Using a similar approach, Coffen and co-workers<sup>83</sup> synthesized a simple aromatic analog of aranotin, 130 (SCHEME 16). Unfortunately, both 130 and the corresponding epitrisulfide lacked antiviral activity. It is interesting that dienol 129 was extremely insoluble and precluded the recording of an NMR spectrum.

Many other unsuccessful synthetic approaches to epidithia-2,5-piperazinedione have been described, but will not be discussed in detail here. However, these include syntheses<sup>6b,77,78,80,81,84-88,94</sup> of  $\alpha$ -mercapto- $\alpha$ -amino acid derivatives and additions of sulfur nucleophiles to dehydroamino acids and dehydrodipeptides.<sup>71,89-93,95,96</sup>

SCHEME 16

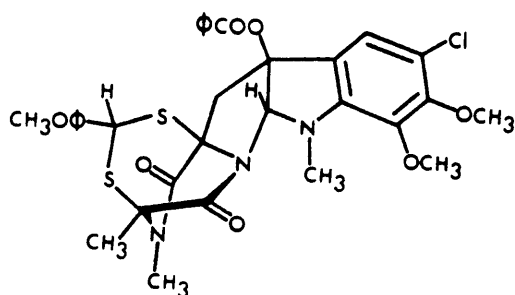


An interesting desthiomethylene analog of gliotoxin (131) was prepared by Ottenheijm and co-workers.<sup>97,98</sup>



Although 131 mimics the three-dimensional structure of an epidithia-2,5-piperazinedione, it lacked the antiviral and antibacterial properties common to the disulfides.

# Total Syntheses

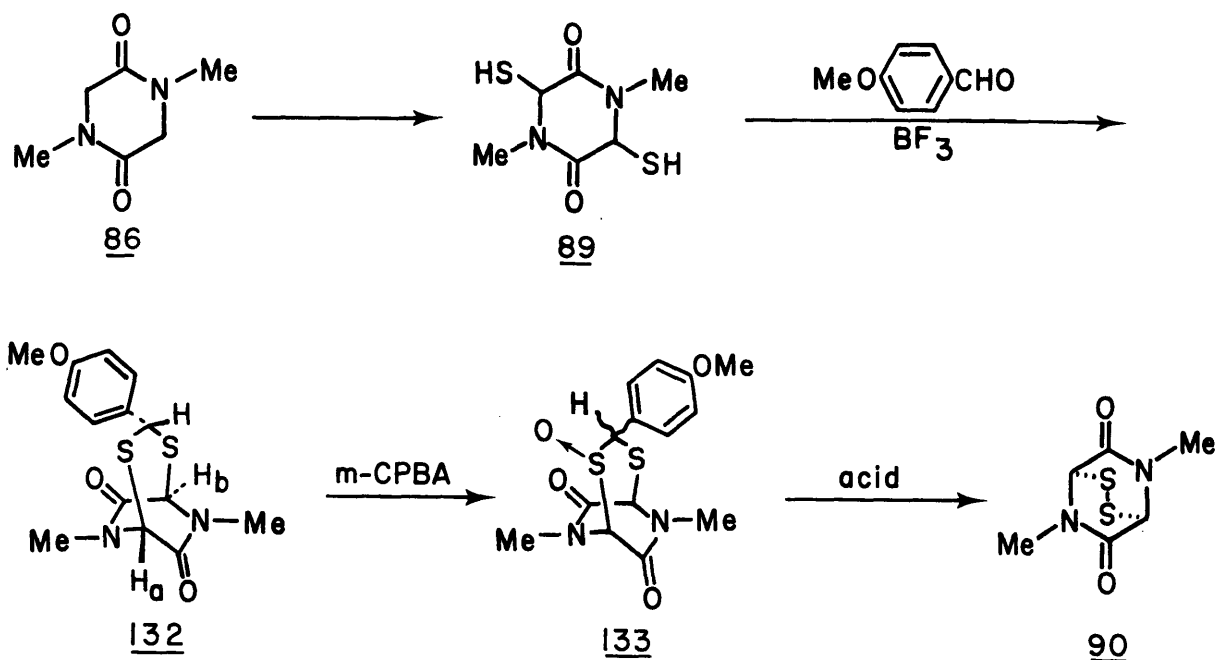


Application of the aforementioned synthetic methods to the synthesis of naturally occurring epidithia-2,5-piperazinediones is difficult. The epidithia-2,5-piperazinedione moiety is extremely unstable under oxidative ( $\text{Br}_2$ , NBS, m-CPBA, etc.), reductive (sodium borohydride, LAH, etc.), and basic (NaOMe, NaOH, etc.) conditions. Only under acidic conditions, is it acceptably stable. Therefore, once this delicate moiety is introduced into a synthetic intermediate, it is not expected to remain intact during subsequent synthetic transformations. Consequently, the disulfide should be constructed at the end of the synthesis.

Kishi and co-workers<sup>59,100</sup> have devised an ingenious and versatile method for the protection of the disulfide functionality and have exploited this in total syntheses of dehydrogliotoxin,<sup>101</sup> sporidesmins A<sup>102</sup> and B,<sup>103</sup> gliotoxin<sup>105</sup> and hyalodendrin.<sup>104,106</sup>

3,6-unsubstituted-2,5-piperazinediones (i.e., 86) are transformed into cis and trans dimercaptans (i.e., 89) using the Trown<sup>58</sup> method, and subsequently protected as the p-anisaldehyde dithioacetal (i.e., 132). The thioacetal is stable under acidic, basic or reductive conditions. Furthermore, functionalization at the bridgehead positions (132, Ha, H<sub>b</sub>) can be achieved in a regiospecific manner. Treatment of 132 with n-butyllithium produces the bridgehead anion which can be alkylated with a variety of alkylating or acylating reagents. A single diastereomer is obtained from this

SCHEME 17



procedure. This has been rationalized<sup>59</sup> as follows: the stereochemistry of the anisaldehyde residue determines a conformation<sup>107</sup> (i.e., for **132**) which brings the sulfur atom adjacent to  $\text{H}_b$  closer to the neighboring amide-carbonyl than the sulfur adjacent to  $\text{H}_a$ . This interaction makes  $\text{H}_b$  more acidic than the  $\text{H}_a$  and thus results in regiospecific bridge-head carbanion formation.

The dithioacetal can be smoothly cleaved to the corresponding epidithia-2,5-piperazinedione in two steps: oxidation of **132** with *m*-CPBA affords sulfoxide **133** which, upon treatment with acid (e.g.,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ,  $\text{BCl}_3$ ,  $\text{H}_2\text{SO}_4$  or  $\text{HClO}_4$ ), directly furnishes the epidithia-2,5-piperazinedione **90**. In the cleavage reaction of the sulfoxide (**133**), resonance stabilization of the intermediate carbonium ion provided by the

p-methoxyaryl group is crucial. Dithioacetals derived from formaldehyde, benzaldehyde or acetaldehyde, do not undergo this cleavage reaction.

The versatility of Kishi's disulfide protection is illustrated in the following total syntheses. A similar disulfide protection was also exploited by Harrison and co-workers at Syntex in a synthesis of holomycin<sup>108</sup>

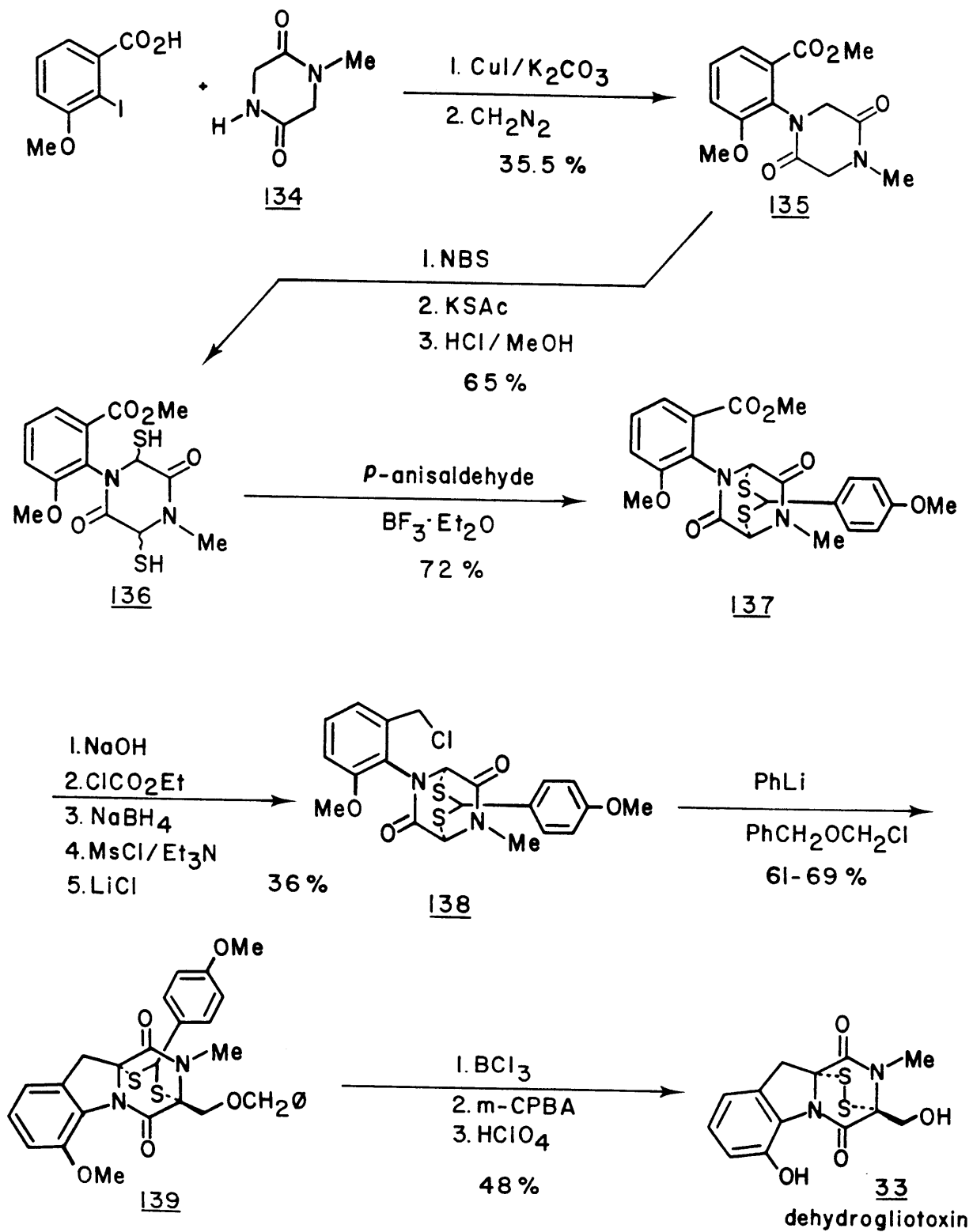
d,l-Dehydrogliotoxin was synthesized<sup>101</sup> as illustrated in SCHEME 18. Heating piperazinedione 134 with 2-iodo-3-methoxybenzoic acid in the presence of a copper catalyst furnished N,N-disubstituted piperazinedione 135. Sulfenylation according to Trown<sup>58</sup> affords a cis, trans mixture of dimer-captans 136 which are converted into a 1:1 mixture of thioacetal diastereomers 137. The esters are reduced to the primary chlorides 138, in four steps. Either diastereomer of 138 could be converted into 139 by an elegant one-pot procedure involving addition of 2.5 equivalents of phenyllithium to a mixture of 138 and benzylchloromethyl ether. The stereochemistry of the anisaldehyde residue of each diastereomer determines the order in which intramolecular cyclization and benzyloxymethylation takes place at the bridgehead positions. Boron trichloride treatment of 139 cleaved both the benzyl and methyl ethers. Subsequent oxidation to the sulfoxide with m-CPBA followed by acid treatment afforded d,l-dehydrogliotoxin (33).

An interesting modification of Trown's<sup>58</sup> procedure was



## SCHEME 18

## Total Synthesis of d,l-Dehydrogliotoxin



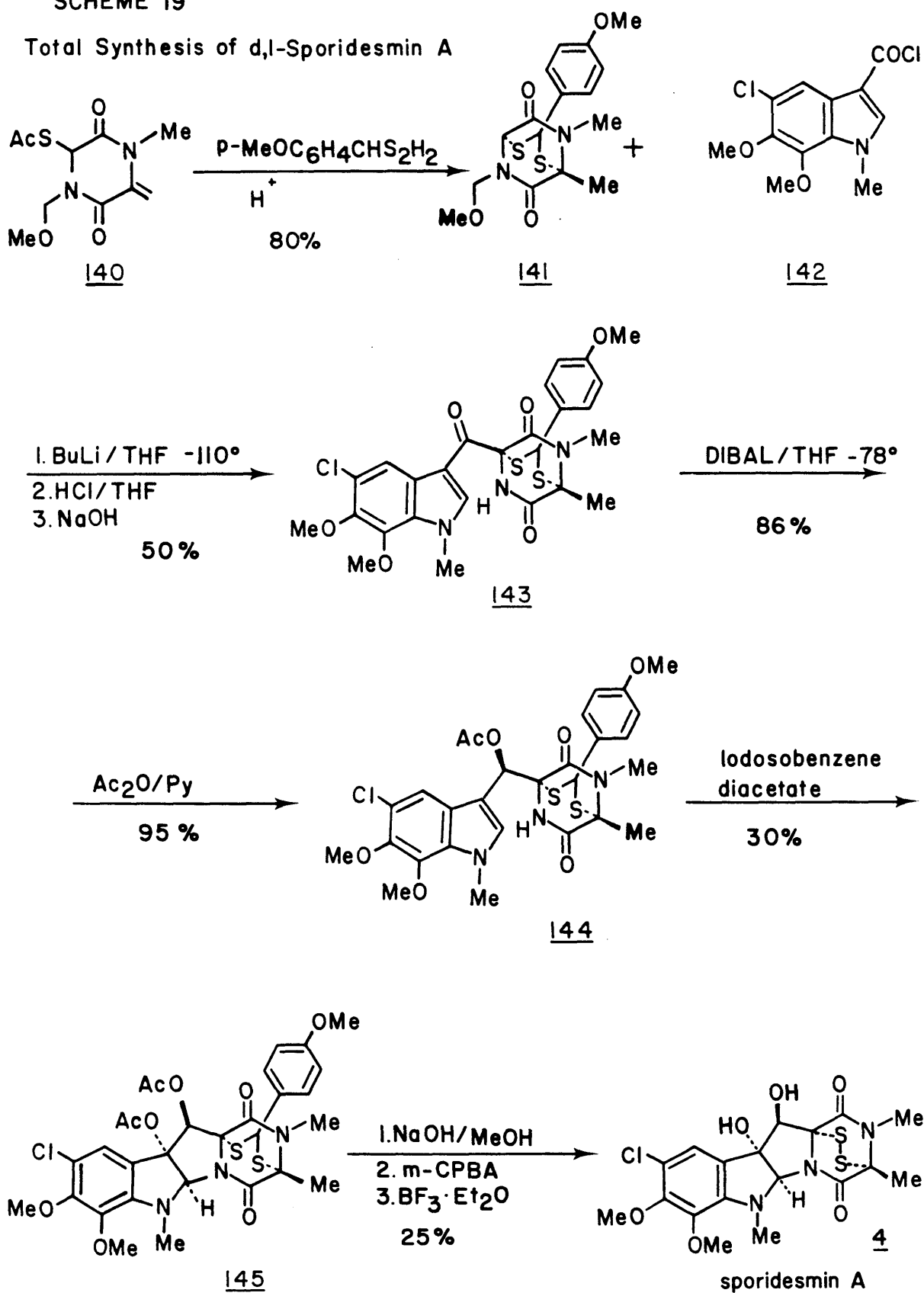
used for the preparation of dithioacetal 141 in the synthesis of sporidesmin A<sup>102</sup> (SCHEME 19). NBS bromination of 4-methoxymethyl-1,6-dimethyl-2,5-piperazinedione followed by potassium thioacetate workup afforded thioacetate 140 in 70% yield. Conversion of 140 into dithioacetal 141 was achieved by treatment with HCl in methanol followed by the trithiane derivative of p-anisaldehyde and boron trifluoride etherate. The carbanion derived from 141 was treated with acid chloride 142 to afford 143 after removal of the amide protecting group. The ketone of 143 was stereospecifically reduced to the alcohol by diisobutylaluminum hydride. Complex formation of the reducing agent and the amide N-H is thought to be responsible for the selectivity in the reduction step. Acetylation afforded 144 which was oxidatively cyclized to the eserine 145 by treatment with iodosobenzene diacetate. Hydrolysis of the acetates and cleavage of the dithioacetal in the standard manner furnished d,1-sporidesmin A(4).

Sporidesmin B<sup>103</sup> (5) was synthesized in a similar fashion by reducing acetate 144 to the methylene derivative with sodium cyanoborohydride. Analogously, oxidative cyclization and deprotection afforded d,1-sporidesmin B.

Gliotoxin<sup>105</sup> was synthesized using a solvent-dependent Michael addition of dithioacetal 147 to arene oxide 146. With Triton B as catalyst, a 1:3 mixture of 148:149 was realized in methylene chloride. The ratio of 148 to 149 was reversed (3:1) in DMSO. This dramatic solvent effect has been

## SCHEME 19

## Total Synthesis of d,l-Sporidesmin A



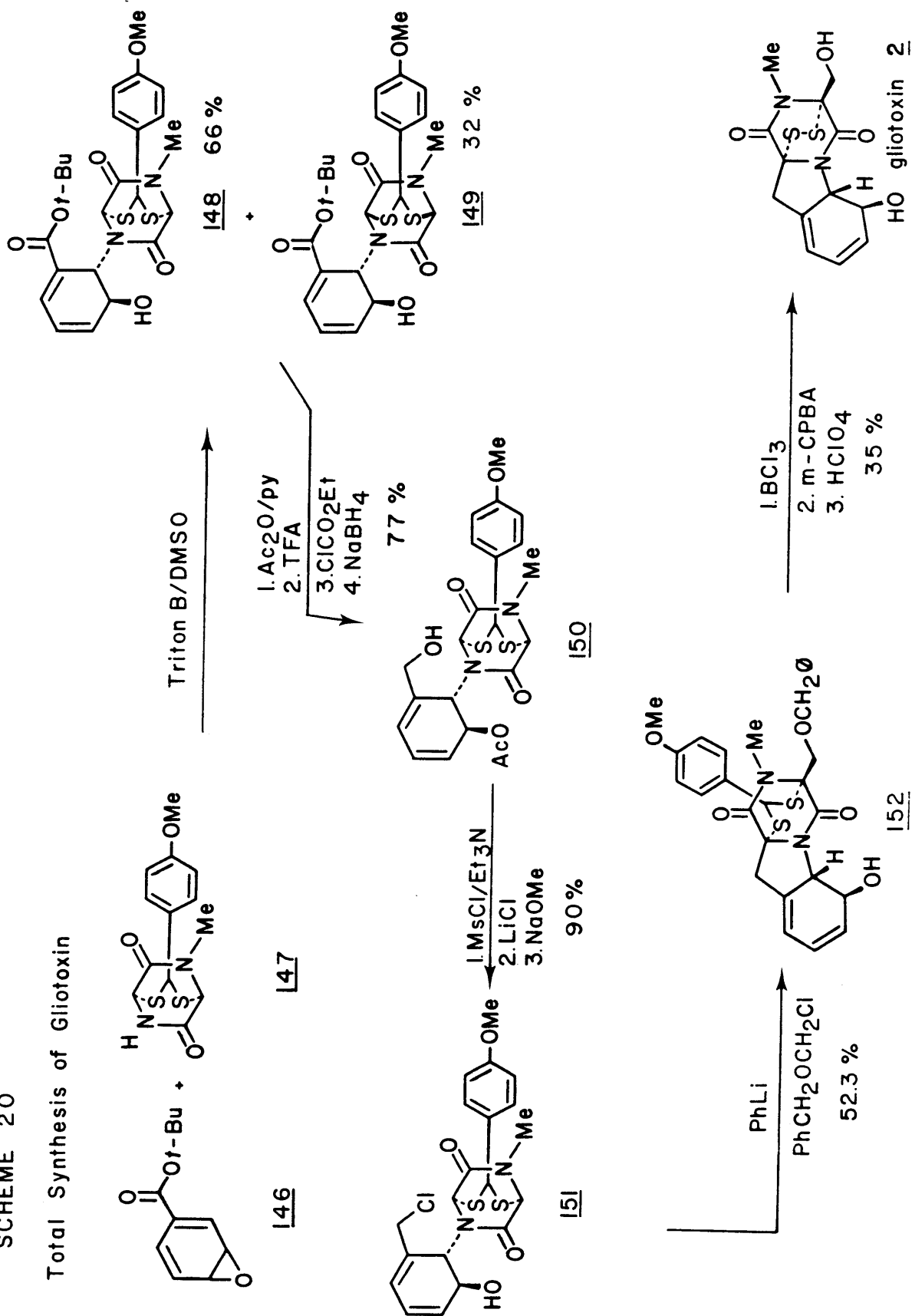
rationalized to involve dipole interactions in the transition state of the 1,4-addition. Conversion of 148 to gliotoxin (2) was achieved in a manner analogous to that for dehydrogliotoxin (33, SCHEME 18). Likewise, cyclization and benzyloxymethylation of 151 was achieved in a one-pot procedure. Optically active (+)-gliotoxin was similarly synthesized<sup>59</sup> by chemical resolution of dithioacetal 147.

Although the dithioacetal protecting group for epidithia-2,5-piperazinedione syntheses proved general, there still remained problems which prevented scale-up of these reactions. Namely, the bridgehead carbanions derived from the dithioacetal have a short half-life (ca. 10 min. at -78°C). In addition, cleavage of the dithioacetal monosulfoxides required subtle and carefully controlled conditions.<sup>59</sup> An alternative approach<sup>59,104</sup> was developed by Kishi and co-workers and is illustrated in a total synthesis of d,l-hyalodendrin (SCHEME 21),

Dithiol 89 was protected as the bis-methoxymethylthio ether 155 by treatment with potassium t-butoxide and excess chloromethyl methyl ether. A one-pot, cis dialkylation of 155 was achieved by sequential treatment with 2.3 equivalents of lithium diisopropylamide, benzylbromide and bromomethyl methyl ether to furnish a single isomer 157. Conversion of 157 to d,l-hyalodendrin (53) was realized by boron trichloride cleavage of the sulfur protection, oxidation to the disulfide and cleavage of the methyl ether. The low yield of the last three steps is due to competitive demethylation and

SCHEME 20

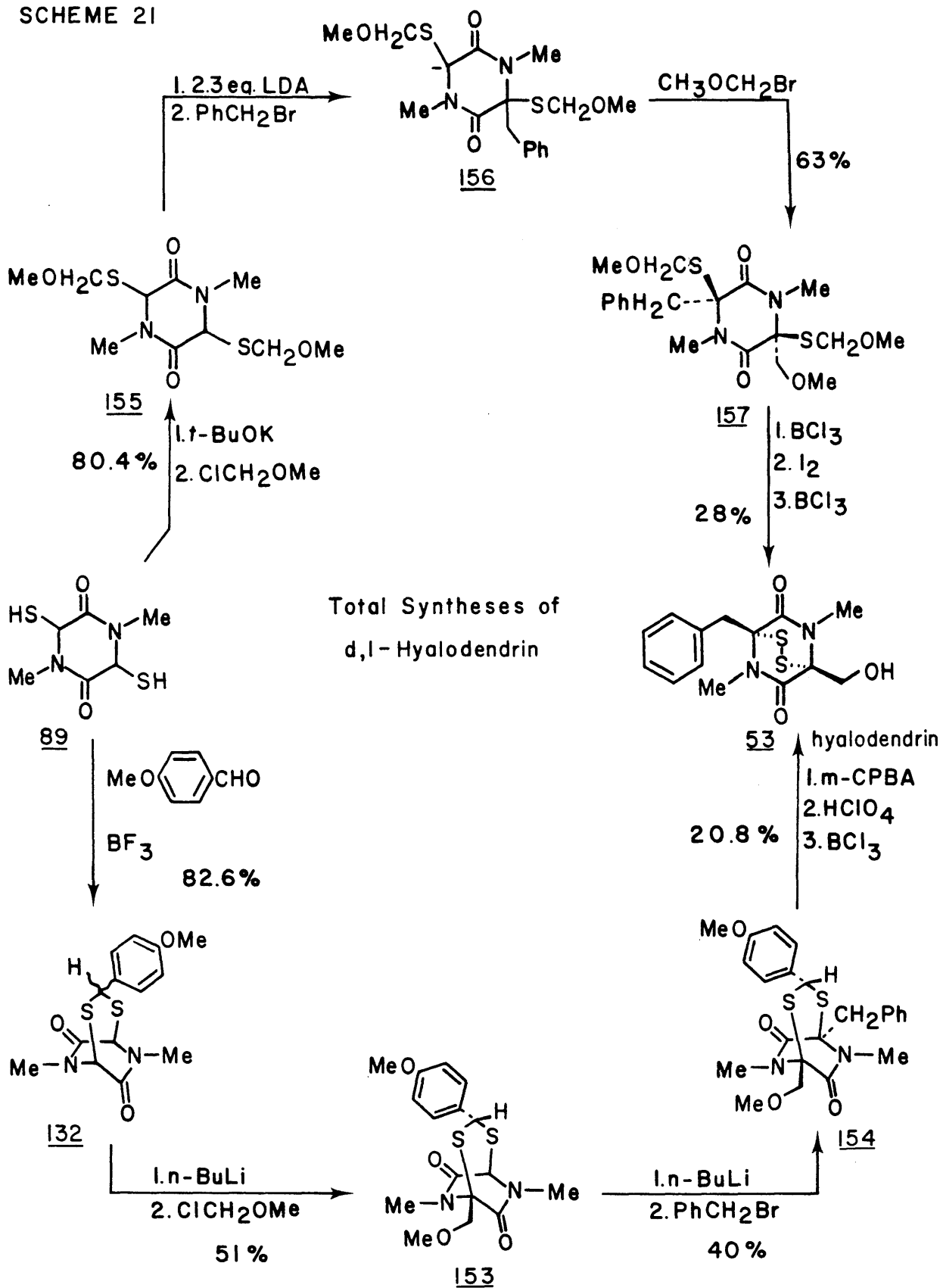
Total Synthesis of Gliotoxin



and demethoxymethylation with boron trichloride,

A synthesis of d,l-hyalodendrin using the Kishi dithioacetal approach was reported by Strunz and Kakushima<sup>106</sup> and is illustrated in SCHEME 21.

SCHEME 21



# **Prolylproline Anhydride**

## **Studies**

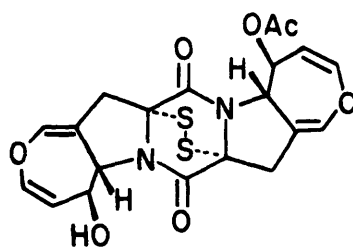
One creates from nothing.

If you try to create from something  
you're just changing something.

So in order to create something you  
first have to be able to create nothing.



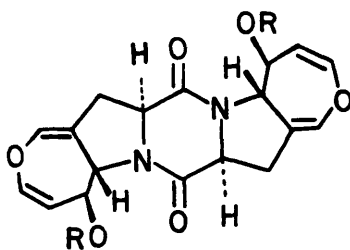
The unique structural features of aranotin 34 pose an



aranotin

interesting challenge to the synthetic organic chemist.

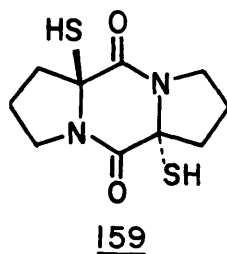
In particular, the bis-enolether moieties are sensitive to acid ( $\text{pH} < 6$ ) and oxidation. As noted previously, the disulfide functionality is extremely unstable to oxidative, reductive and basic conditions. Therefore, these sensitive functionalities must be assembled in a mild fashion and in a stereocontrolled manner. Since the bis-enol ethers are stable to base, it was thought that introduction of the sulfur atoms into a compound such as 158<sup>109</sup>



158

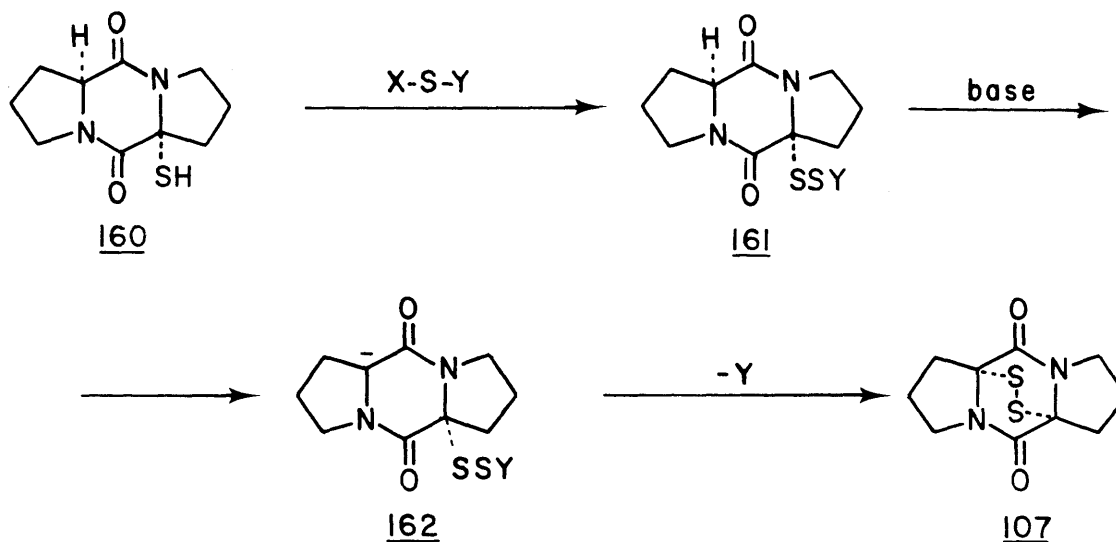
using a modification of Schmidt's<sup>65,66</sup> sulfenylation procedure would provide success. Schmidt's procedure provided a 43% crude yield of epidithio prolylproline anhydride by sequentially sulfenylating the anion derived from the 2,5-piperazinedione. In my own efforts at reproducing this result,

I obtained purified yields of 17-20%. The low yield of this procedure is presumably due to loss of product formed as the trans-dimercaptan 159.



Our approach, utilizing the proline model system is described herein. It was felt that connecting the two sulfurs together prior to formation of the second carbon-sulfur bond would obviate the low stereoselectivity of Schmidt's approach (SCHEME 22)

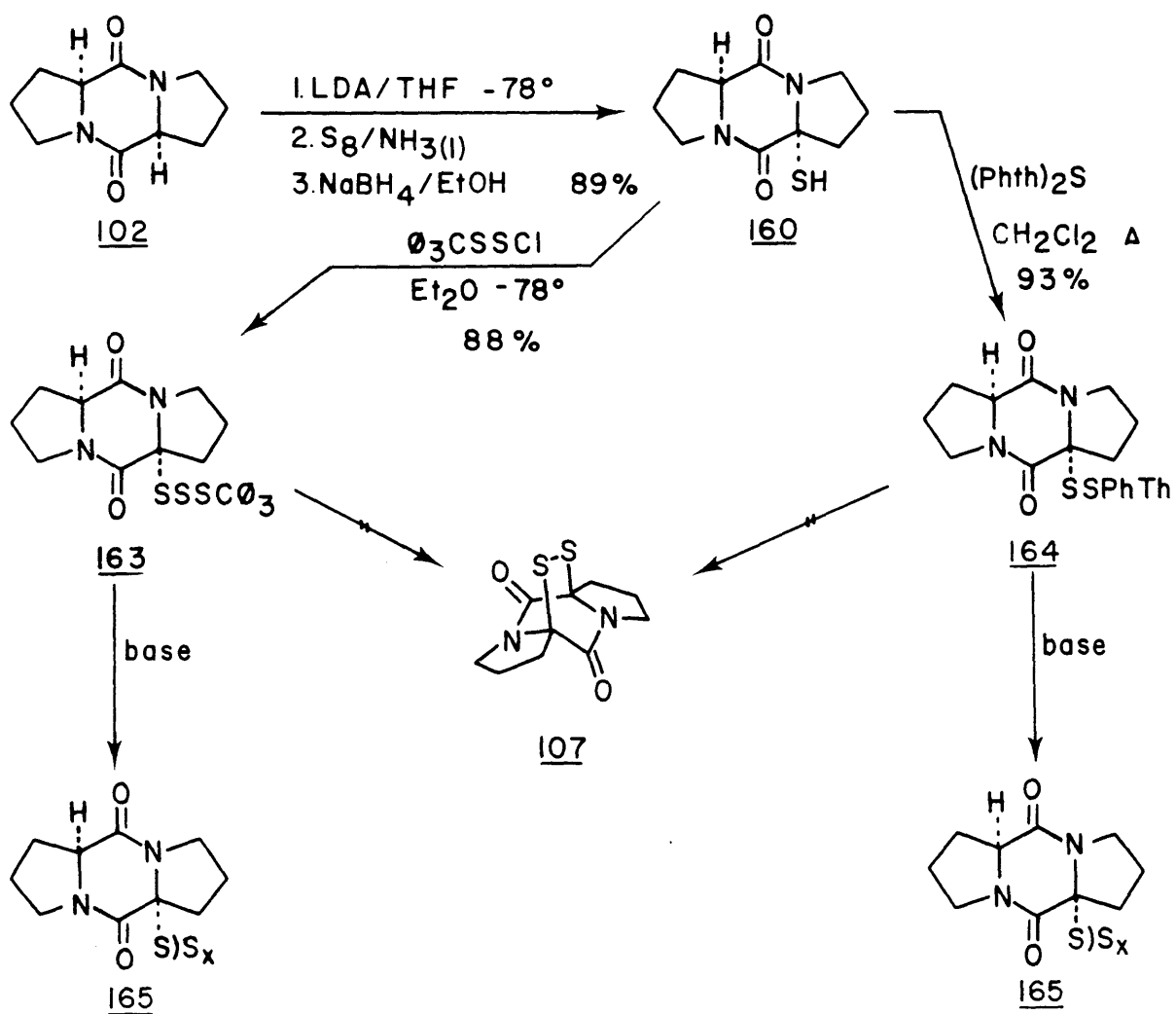
SCHEME 22



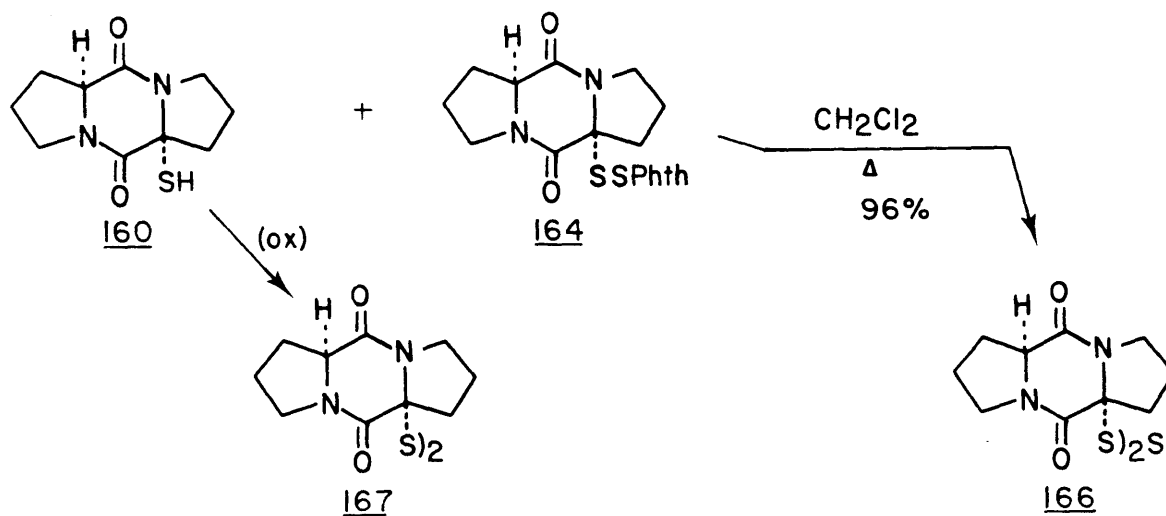
The thiol 160 was efficiently prepared by minor modification of Schmidt's procedure. Coupling with the readily available sulfur transfer reagents N,N'-thio-bisphthalimide<sup>110-114</sup> and triphenylmethyldithio chloride<sup>114b</sup> afforded in high yield the desired intermediates 163 and 164 (SCHEME 23).

Unfortunately, treatment of either 163 or 164 with a variety of strong, non-nucleophilic bases (LDA, tert-BuOK, lithium tetramethylpiperidide, KH, lithium hexamethyl disilazane, etc.) afforded mostly the oily, dimer polysulfide 165 and none of the desired epidithio-2,5-piperazinedione. The number of sulfur atoms contained in 165 was not ascertained. Authentic samples of both the disulfide 167

SCHEME 23



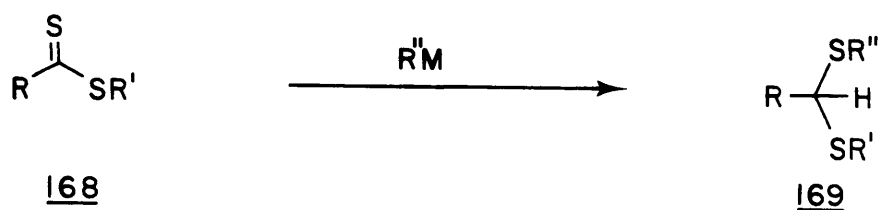
SCHEME 24



and trisulfide 166 were prepared (SCHEME 24). These compounds had similar NMR and IR spectra and could not be separated by TLC. Compound 165 also had similar properties, and no distinctions could be made. These results indicated that the sulfur functionalities of 161 reacted faster with base than deprotonation. As evidence, reaction mixtures quenched with D<sub>2</sub>O incorporated no deuterium at the 6-methinyl position.

At this point, we searched for a more stable sulfur containing functionality that would not react rapidly with the base, but still sulfenylate the anion derived from the 2,5-piperazinedione.

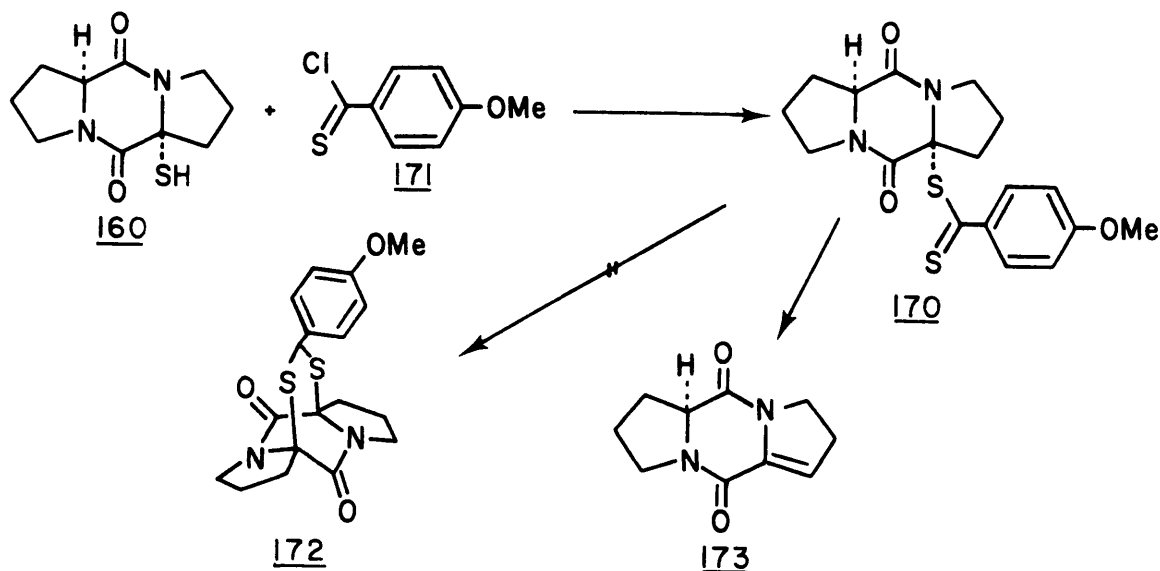
Recently, Masson and co-workers<sup>115</sup> have shown that thionothio esters react with Grignard reagents to form, after workup, the corresponding dithioacetals:



It was hoped that a similar intramolecular reaction might take place with a thionothio ester derived from the 2,5-piperazinedione. Thus, the thionothio ester 170 was

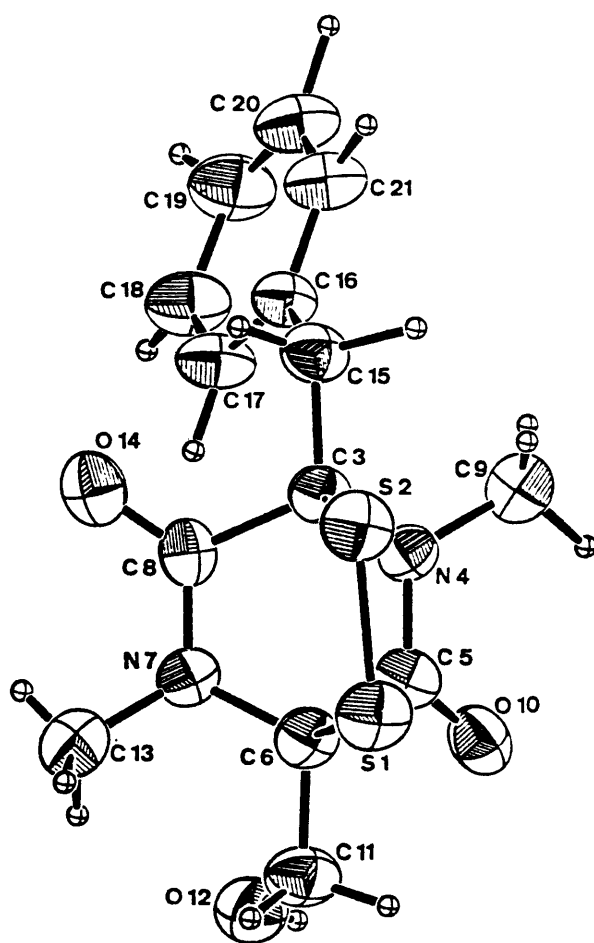
prepared by coupling thiol 160 with the (difficult to prepare) thiono acid chloride<sup>116</sup> 171 (SCHEME 25). However, this compound proved to be difficult to purify, as it was unstable. In a matter of hours at room temperature, significant amounts of dehydro compound 173 was formed. Attempted treatment of this unstable thionothio ester with strong base at low temperature afforded none of the desired Kishi-type dithioacetal, but only dehydro compound 173.

SCHEME 25



It was also realized that, even if the desired dithioacetal was formed, the harsh conditions required for cleavage to the disulfide<sup>100</sup> (m-CPBA oxidation followed by strong acid treatment) would not be compatible with the bis-enolethers of aranotin.

At this point the decision was made to abandon the proline model studies and investigate a new approach for the synthesis of the epidithia-2,5-piperazinedione moiety.

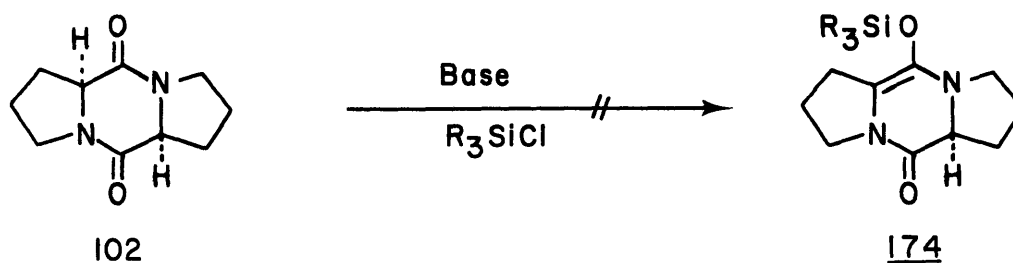


## Total Synthesis of Hyalodendrin & Gliovictin



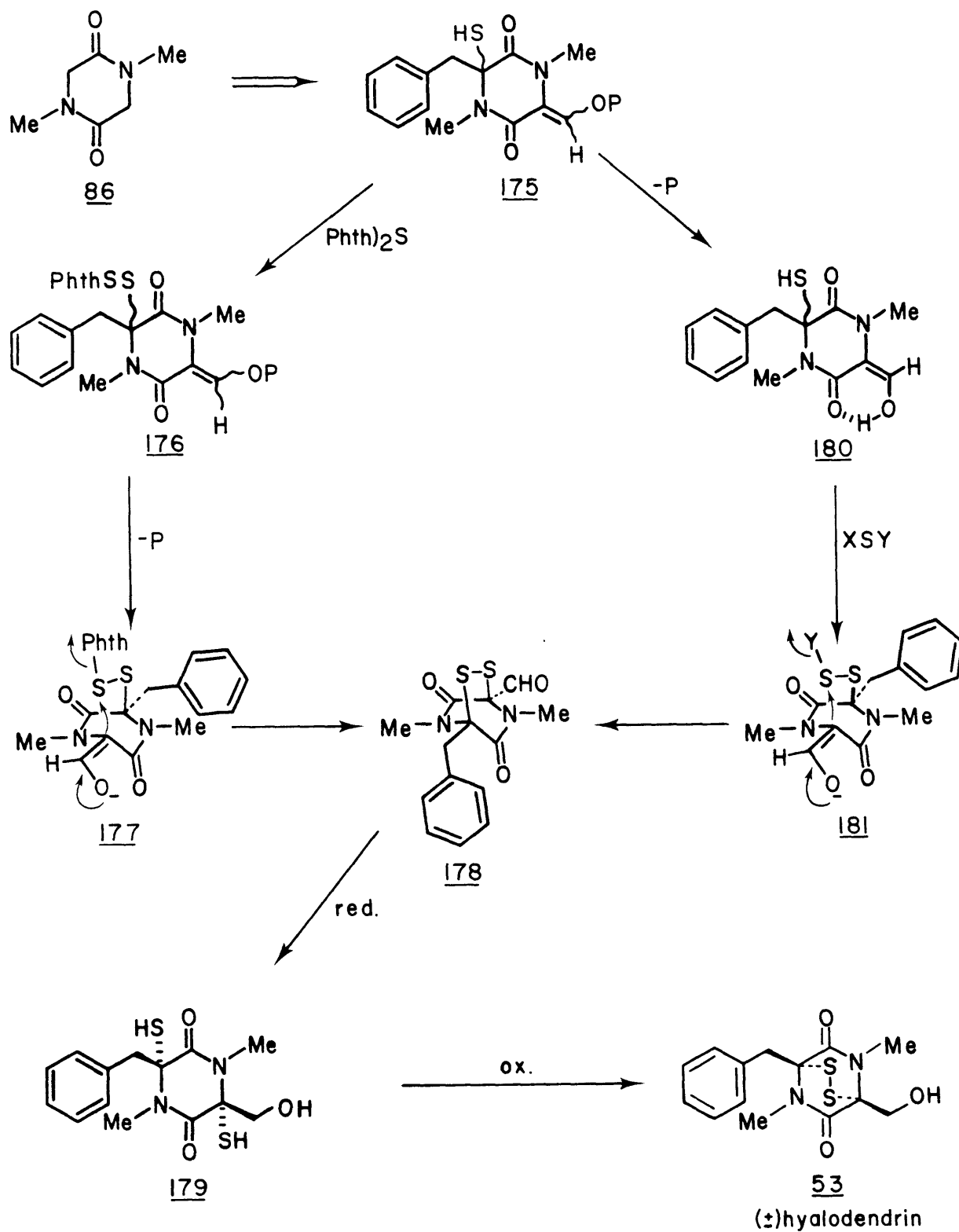
The difficulties encountered in generating the enolate from activated disulfides (e.g., 163, 164) led to the development of a strategy in which the enolate, or a protected form thereof, could be introduced into a synthetic intermediate prior to construction of the activated disulfide. Subsequent release of the enolate could, in principle, cyclize to form the desired epidithia-2,5-piperazinedione.

Efforts to protect the enolate derived from 102 as its silyl enol ether (e.g., 174) were unsuccessful. Only the



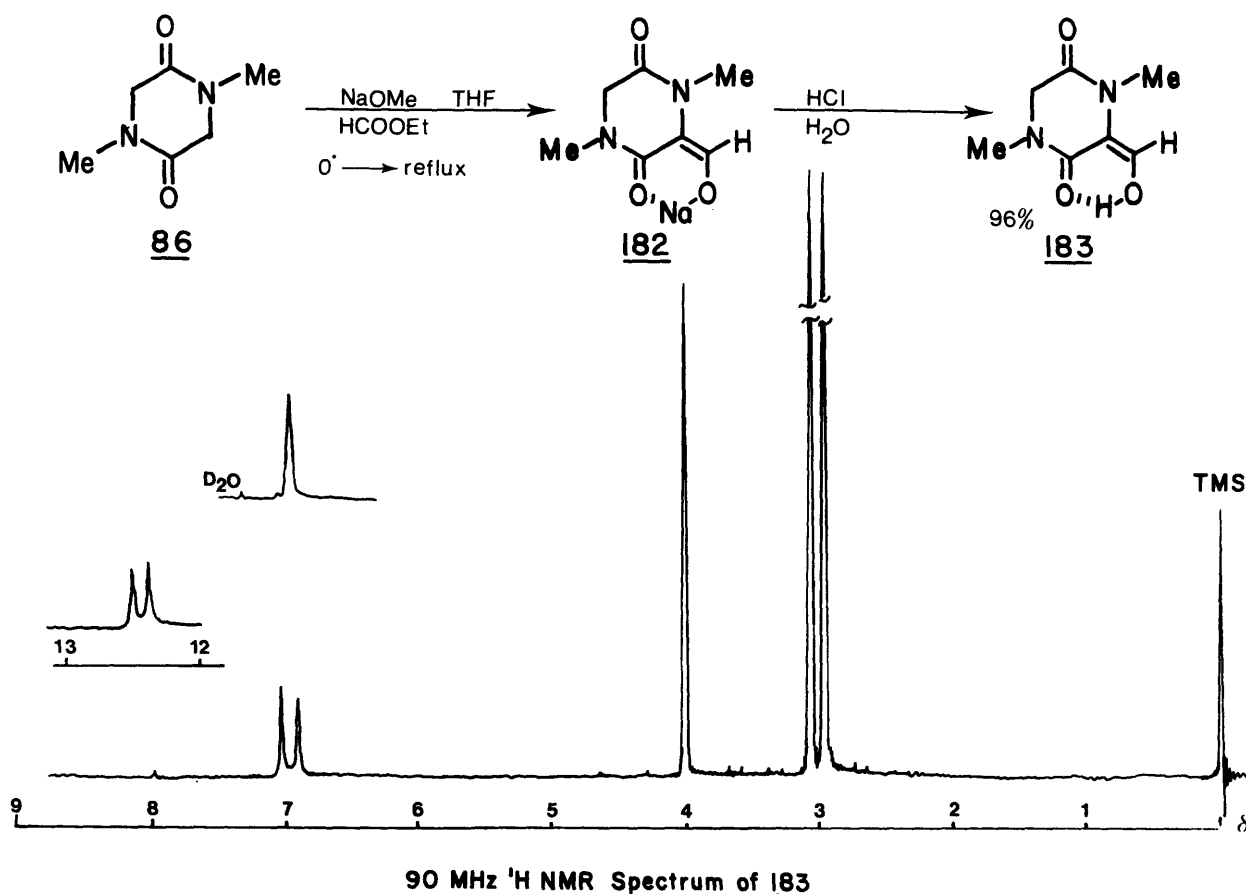
starting material (102) was recovered from attempted silylation of 102.

As an alternative, hyalodendrin (53) was chosen as the target molecule for a new strategy (SCHEME 26). Starting with the simple 1,4-dimethyl-2,5-piperazinedione (86), benzyl, mercapto and formyl (as protected enol-ether) groups are introduced forming 175. Coupling mercaptan 175 with N,N'-thiobisphthalimide would provide 176, which upon removal of the protecting group would be able to cyclize via enol 177 to afford



## Monoformylation

SCHEME 27



epidithia-2,5-piperazinedione **178**. Subsequent reduction of the aldehyde and disulfide functionalities followed by mild oxidation would provide d,l-hyalodendrin (**53**). Alternatively, deprotection of **175** prior to coupling with N,N'-thiobisphthalimide or a variety of other, more reactive sulfur transfer reagents (X-S-Y) could also, in principle, provide sulfur directed cyclization (via **181**) to **178**.

Attempts to benzylate sarcosine anhydride (86) with LDA and benzyl bromide led to complex mixtures. However, formylation of 86 using a modified W. S. Johnson procedure<sup>117</sup> led to clean monoformylation (SCHEME 27) producing 1,4-dimethyl-3-formyl-2,5-piperazinedione 183 in 96% yield.<sup>118</sup> Although excess base and ethylformate were used in this procedure, only monoformylation occurred since the sodium salt 182 was virtually insoluble in THF, and precipitated before further reaction could take place. Compound 183 can be produced in large quantities, is crystalline, stable and soluble in most organic solvents (THF, CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, etc.) as well as in water and lower alcohols. The NMR spectrum of 183 is shown along with SCHEME 27. The characteristic coupling of the enolic O-H to the formyl proton (12.5 and 7.0 $\delta$ , respectively, J=11Hz) is in agreement with the assigned structure. This characteristic NMR pattern made subsequent enol-containing intermediates easy to identify.

The reactions of mercaptans with various sulfur transfer reagents (see SCHEME 26, X-S-Y) has been studied in detail. From these studies,<sup>111-114,119,122</sup> it was expected that the mercaptan functionally of 180 would couple with a variety of sulfur transfer reagents (X-S-Y, SCHEME 26) to provide 181. However, less is known about the reactivity of carbon nucleophiles towards the sulfur transfer reagents.<sup>120,121,123</sup> Therefore, the reactivity of the formyl moiety of 183 towards some sulfur transfer reagents was examined.

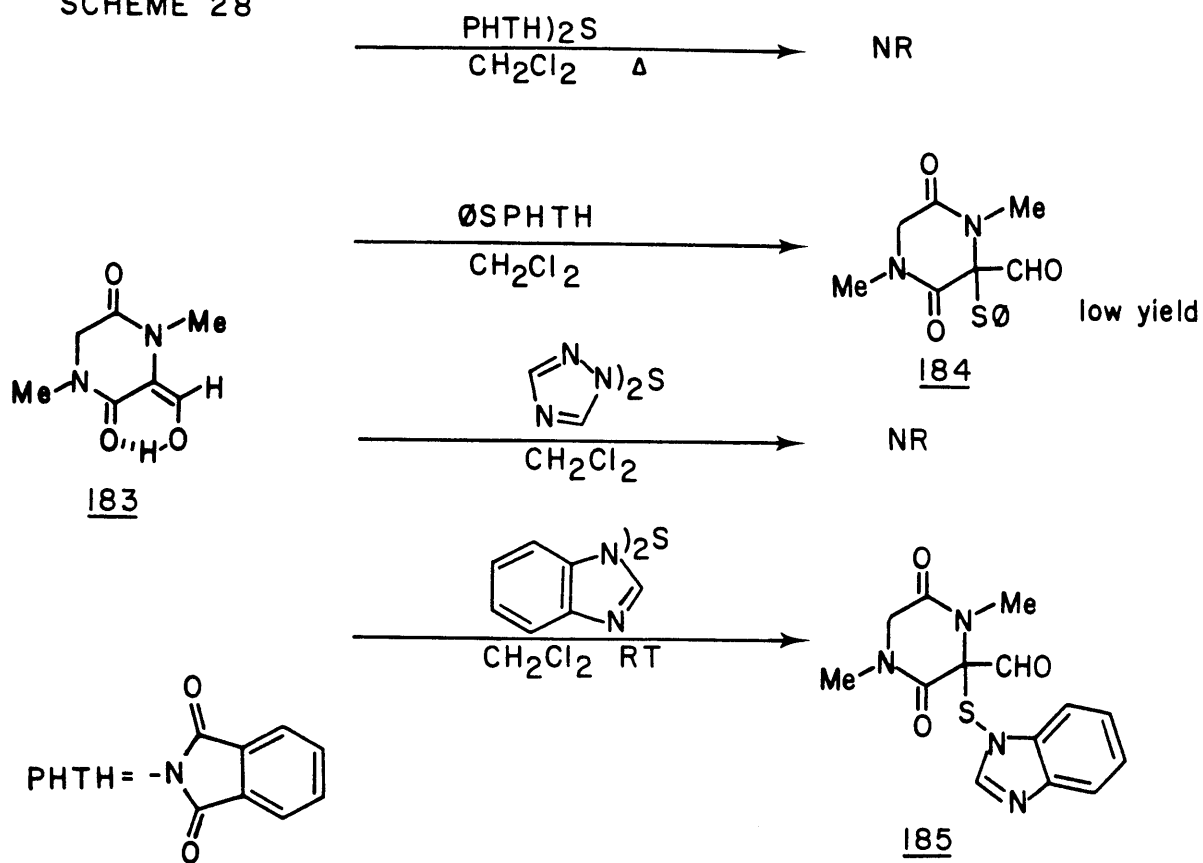
Harpp<sup>119</sup> has found that the order of reactivity of sulfur transfer reagents 186-189 towards thiols, amines and alcohols, roughly follows the order of the pKa of the conjugate

acids of the azole leaving group. The reaction (e.g. with thiols) is thought to involve protonation of the heterocycle followed by nucleophilic attack at sulfur with concomitant displacement of the neutral azole leaving group. Accordingly, the succinimide (190) and phthalimide (191) reagents were found to be the least reactive.<sup>119</sup> The shelf stability of these reagents, however, follows the reverse order. In this regard, the phthalimido reagents can be used to prepare stable unsymmetrical phthalimido disulfides (e.g., 164, 176). The reactivity of the azole reagents precludes their use<sup>119</sup> in preparing unsymmetrical azole disulfides and are best employed for in situ sulfur transfer (i.e., SCHEME 26,  $180 + X-S-Y \rightarrow 181$ ),

SCHEME 28 shows the reaction of 183 with some sulfur transfer reagents. N,N'-thiobisphthalimide (191) was unreactive toward 183 when heated in methylene chloride at reflux for prolonged periods of time. The NMR spectrum of 183 + 191 indicated a 1:1 mixture of starting materials. Addition of base (e.g. Et<sub>3</sub>N) did not induce reaction. Phenylthiophthalimide produced a very small amount of sulfenylated product (184), but complete reaction was not realized. 1,1'-thiobis-1,2,4-triazole (187) was also found to be unreactive towards (183). Somewhat surprisingly, 1,1'-thiobisbenzimidazole (188) cleanly sulfenylated 183 in methylene chloride at room temperature affording aldehyde 185 as an unstable, white foam (half-life in CDCl<sub>3</sub> was ca. 1 hour). The reactivities of the reagents tested towards 183 are therefore in agreement with the reactivity order served by Harpp.<sup>119</sup>

## Sulfur Transfer Reagents

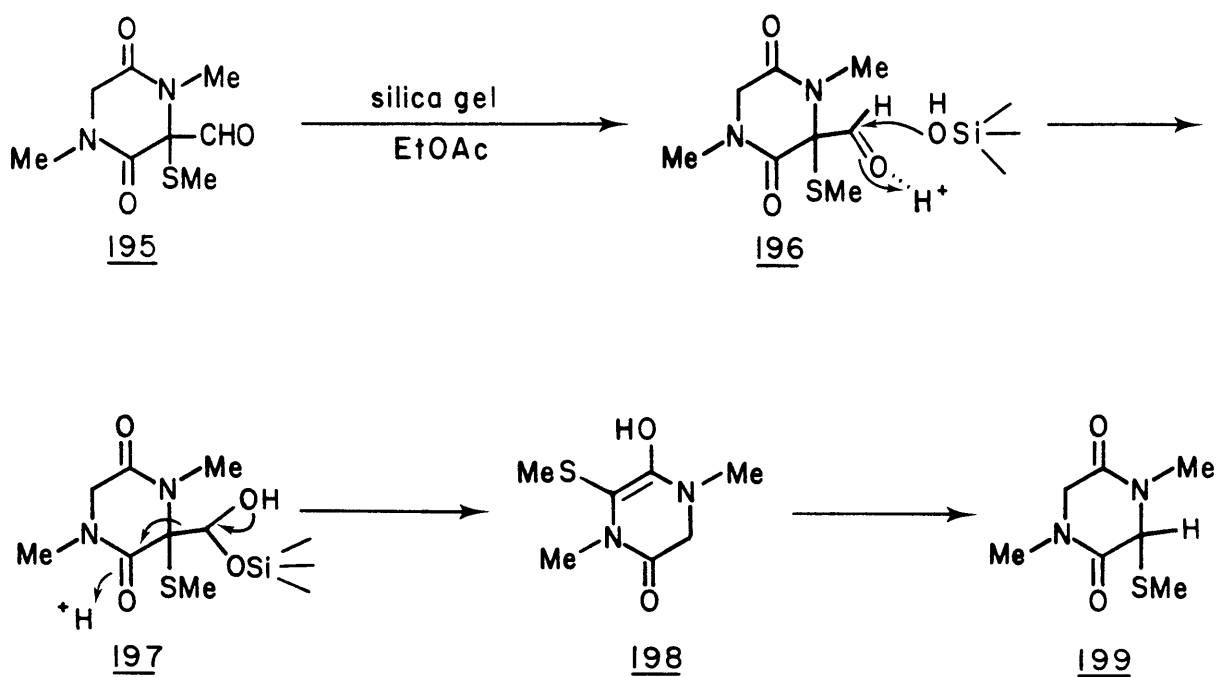
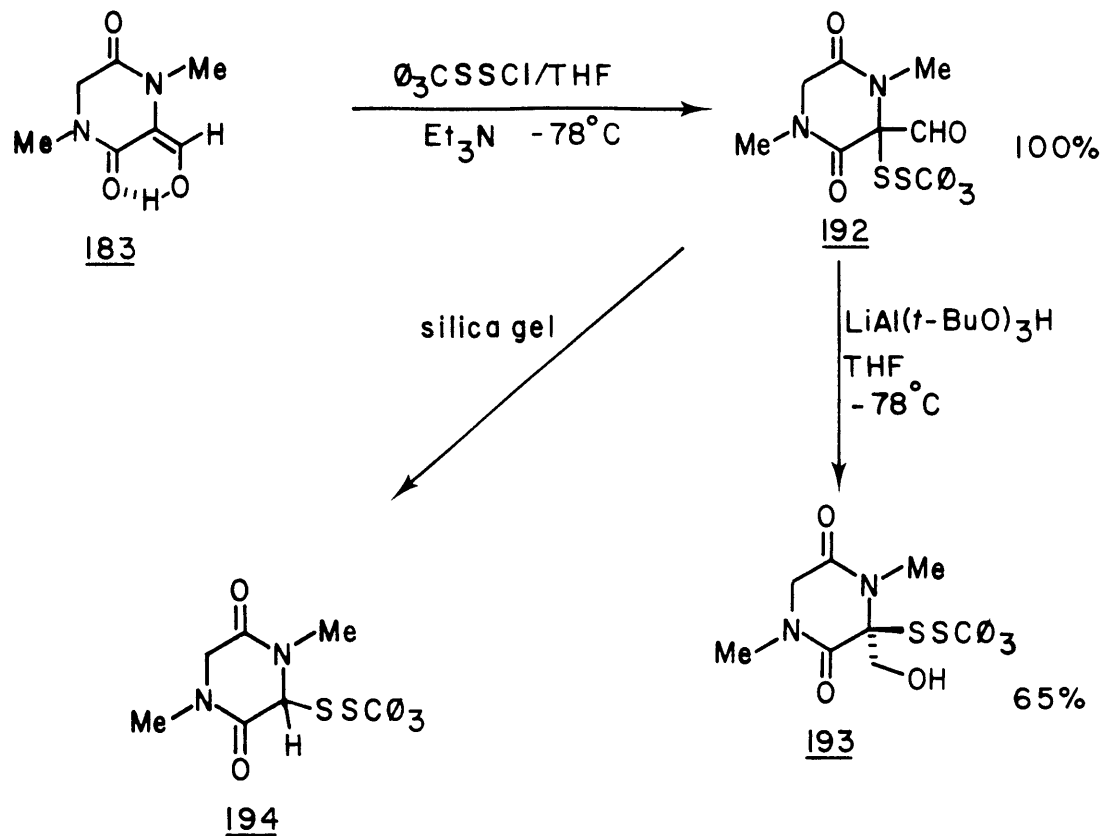
SCHEME 28



### Reactivity of Sulfur Transfer Reagents (D.N. Harpp)

<u>186</u>	<u>187</u>	<u>188</u>	<u>189</u>	<u>190</u>	<u>191</u>
$\text{PK}_a$ 6.95	2.27	5.53	1.6	9.5	8.3
$\text{pK}_b$ 14.52	10.26	12.78	8.64	-	-
<div style="text-align: center;">           ← increasing reactivity         </div>					

A variety of sulfenyl chlorides were also found to react with 183 in the presence of base (typically, triethylamine). Without the addition of base, analysis of reaction mixtures by NMR indicated a mixture of unchanged starting materials. Thus, admixture of 183 with 1 equivalent of triethylamine in THF at low temperature, followed by addition of either methylsulfenyl chloride, phenylsulfenyl chloride, 0-nitro-phenylsulfenyl chloride or triphenylmethyldithio chloride cleanly produced the corresponding  $\alpha$ -mercapto aldehydes (e.g. SCHEME 29, 192) in high yields (>95%). Pure products were obtained simply by filtering off triethylamine hydrochloride and removing the solvent. This turned out to be quite fortunate since, all of the  $\alpha$ -mercapto aldehydes studied were found to be unstable to silica gel chromatography and mild aqueous acid. Upon contact with silica gel, aldehyde 192 suffered deformylation to afford disulfide 194. A similar deformylation occurred with all of the  $\alpha$ -mercaptoaldehydes studied. Spectral data on the deformylated products were consistent with the assigned structures. For example, in the NMR spectrum of 192, the aldehyde proton at  $\delta$ 8.65 disappears after contact with silica gel and a new one-proton singlet appears at  $\delta$ 3.83. In addition, the methylene protons across the ring (6-position) appear as an AB quartet in the deformylated products (i.e., 194, 199) indicating that an asymmetric center is at the 3-position; the methylene protons in 183 appear as a singlet. As further evidence, the  $^{13}\text{C}$  NMR spectrum of 199 shows two  $\text{sp}^2$  carbons (amide)





and five  $\text{sp}^3$  carbons.

A mechanism for this deformylation process is proposed in SCHEME 30. The deformylation reaction is very similar to the stereoselective decarboxylation of 3-carboxy-2,5-piperazinediones reported by Kishi<sup>133a-c</sup> in the total synthesis of echinulin. The mechanism proposed in SCHEME 30 is very similar to the one proposed by Kishi.<sup>133a</sup>

Attention was then focused on reduction of the carbox-aldehyde functionality to the hydroxymethyl moiety present in hyalodendrin. Reduction was found to proceed smoothly with a slight excess of lithium tri-*t*-butoxyaluminum hydride in THF at  $-78^\circ\text{C}$ . Fortunately, in the case of 192, selective reduction of the aldehyde in the presence of the disulfide was realized, affording hydroxymethyl disulfide 193 in 65% yield (SCHEME 29).

Since the formyl moiety of 183 proved suitable for clean introduction of sulfur functionalities into the 2,5-piperazinedione nucleus and could be efficiently reduced to the required hydroxymethyl group, appropriate protection and subsequent functionalization of 183 was investigated.

Introduction of the angular methyl group into ketosteroids has been achieved<sup>117</sup> by formylation of the  $\alpha$ -methylene position, protection of the formyl group as the isopropyl enol ether, alkylation and subsequent mild acid hydrolysis of the enol ether and retro-aldol cleavage of the formyl group. An isopropyl enol ether seemed a likely choice for protection of 183, since introduction of the remaining benzyl and mercaptan groups would

involve strongly basic conditions. The mild acid hydrolysis of the isopropyl enol ether reported by Johnson<sup>117</sup> (i.e. 202→203 with 0.1N HCl in MeOH at 0°C for 1 hour) seemed ideal for generation of 177 or 180 (see SCHEME 26).

Accordingly, the sodium salt of 183 reacted with isopropyl iodide in DMF/THF to afford a mixture of Z and E isomers 200 and 201, respectively (SCHEME 31). The assignment of stereochemistry was based on comparison of the NMR spectra of 183, 200 and 201. When the potassium salt of 183 was prepared and allowed to react with isopropyl iodide under similar conditions, only Z isomer 200 was obtained. Inspection of molecular models shows significant steric compression between the amide carbonyl and enol ether oxygen (electronic lone pair-lone pair repulsion) of isomer 201. Isomer 200 is therefore rationalized to be the thermodynamically more stable isomer.

Surprisingly, enol ethers 200 and 201 proved to be extremely stable to acids (e.g. BCl<sub>3</sub>, BBr<sub>3</sub>, TFA, conc. HCl, HCO<sub>2</sub>H, conc. HBr) and required rather drastic conditions (conc. HCl/MeOH at reflux for 30 minutes) for cleavage to 183. This is in marked contrast to the mild conditions required for hydrolysis of 202 to 203.<sup>117</sup>

Functionalization of 200 proceeded without incident as illustrated in SCHEME 32. Generation of the enolate of 200 with lithium diisopropylamide at -78°C, followed by addition of benzyl bromide afforded 204 in 90% yield. Using a modified

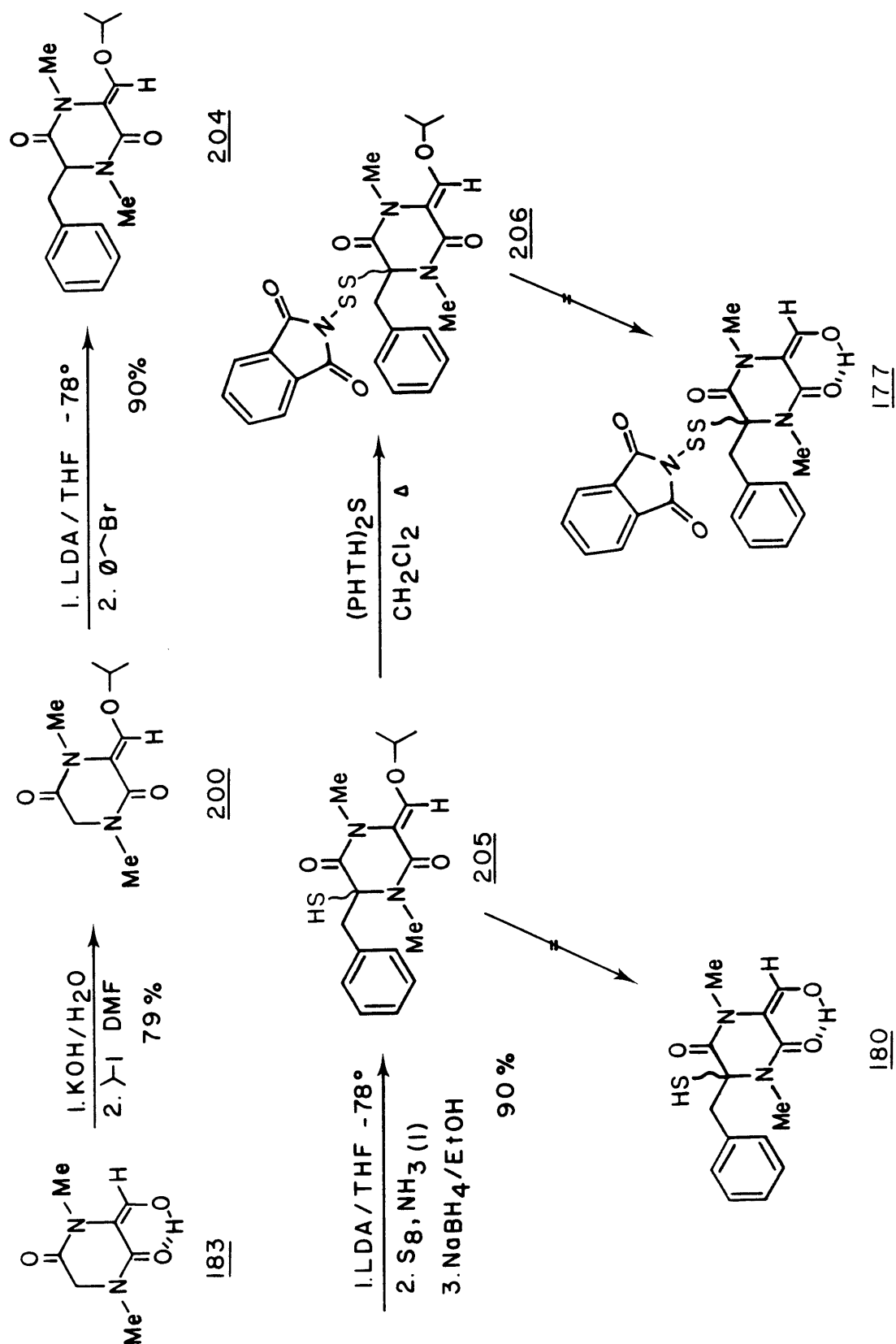


Schmidt procedure,<sup>65,66</sup> 204 was cleanly sulfenylated to afford mercaptan 205 in 90% yield. Coupling mercaptan 205 with N,N'-thiobisphthalimide (191) afforded phthalimido disulfide 206 in modest yield. Unfortunately, neither the desired thiol 180 nor phthalimido disulfide 177 was obtained from 205 and 206 upon treatment with acids. Only complex and unidentifiable mixtures resulted.

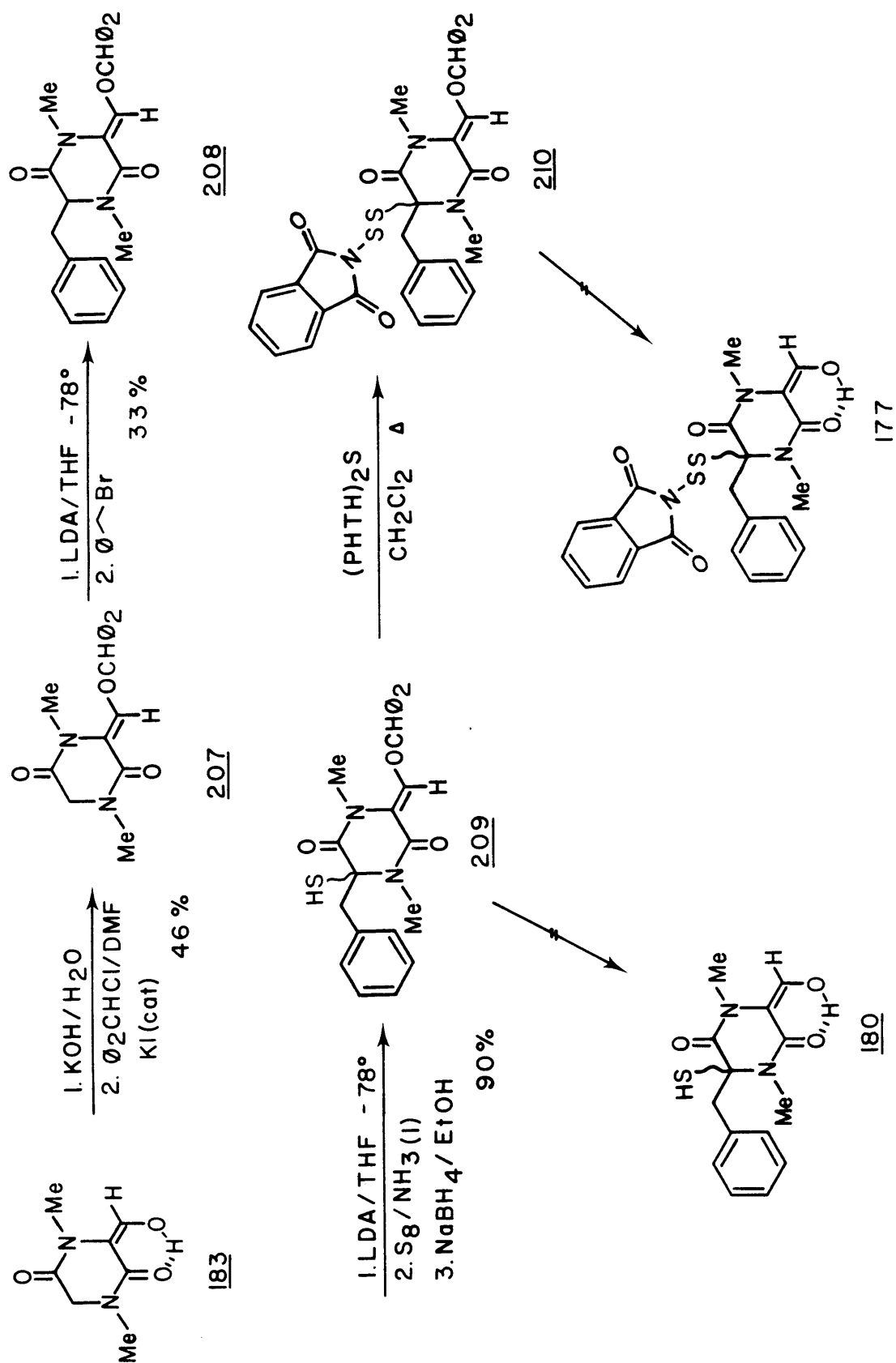
The drastic conditions required for the removal of the isopropyl protecting group were apparently not compatible with the mercapto and phthalimido disulfide functionalities. It was felt that a protecting group capable of forming a stable carbonium ion would facilitate the acidic cleavage of the enol ether and, thus, be possible under milder conditions. Therefore, the benzhydryl enol ether 207 was prepared and the corresponding benzyl (208), mercapto (209) and phthalimido disulfide (210) benzhydryl enol ethers were prepared in somewhat lower yields than the isopropyl series (SCHEME 33). Although cleavage of the benzhydryl enol ether 207 to enol 183 did proceed under slightly milder conditions (conc. HCl/MeOH at room temperature for 30 minutes) than the isopropyl enol ether (cf. SCHEME 31), the desired mercaptan 180 and phthalimido disulfide 177 were not obtained from 209 and 210, respectively. Again, complex mixtures resulted.

Attempts to protect 183 as tetrahydropyranyl (THP), methoxyethoxymethyl (MEM), ethoxyvinyl, p-methoxybenzyl, and t-butyldimethylsiloxy enol ethers were unsuccessful.

SCHEME 32



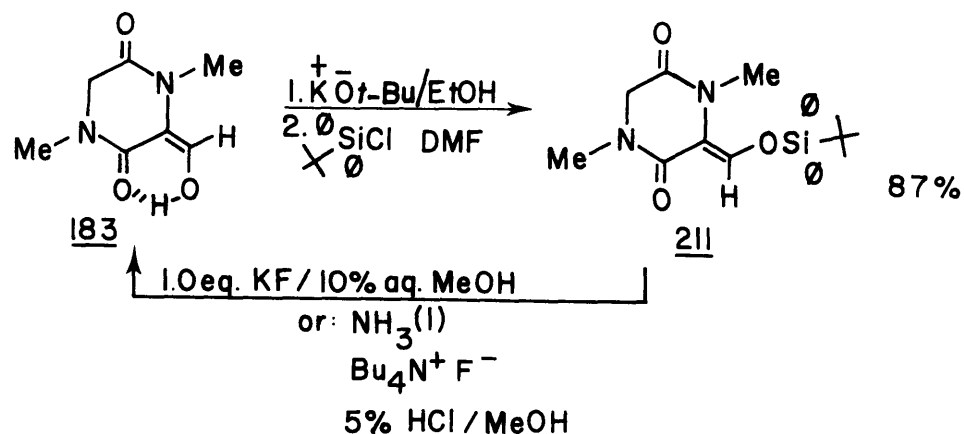
SCHEME 33



## Silyl Protecting Group

87

SCHEME 34



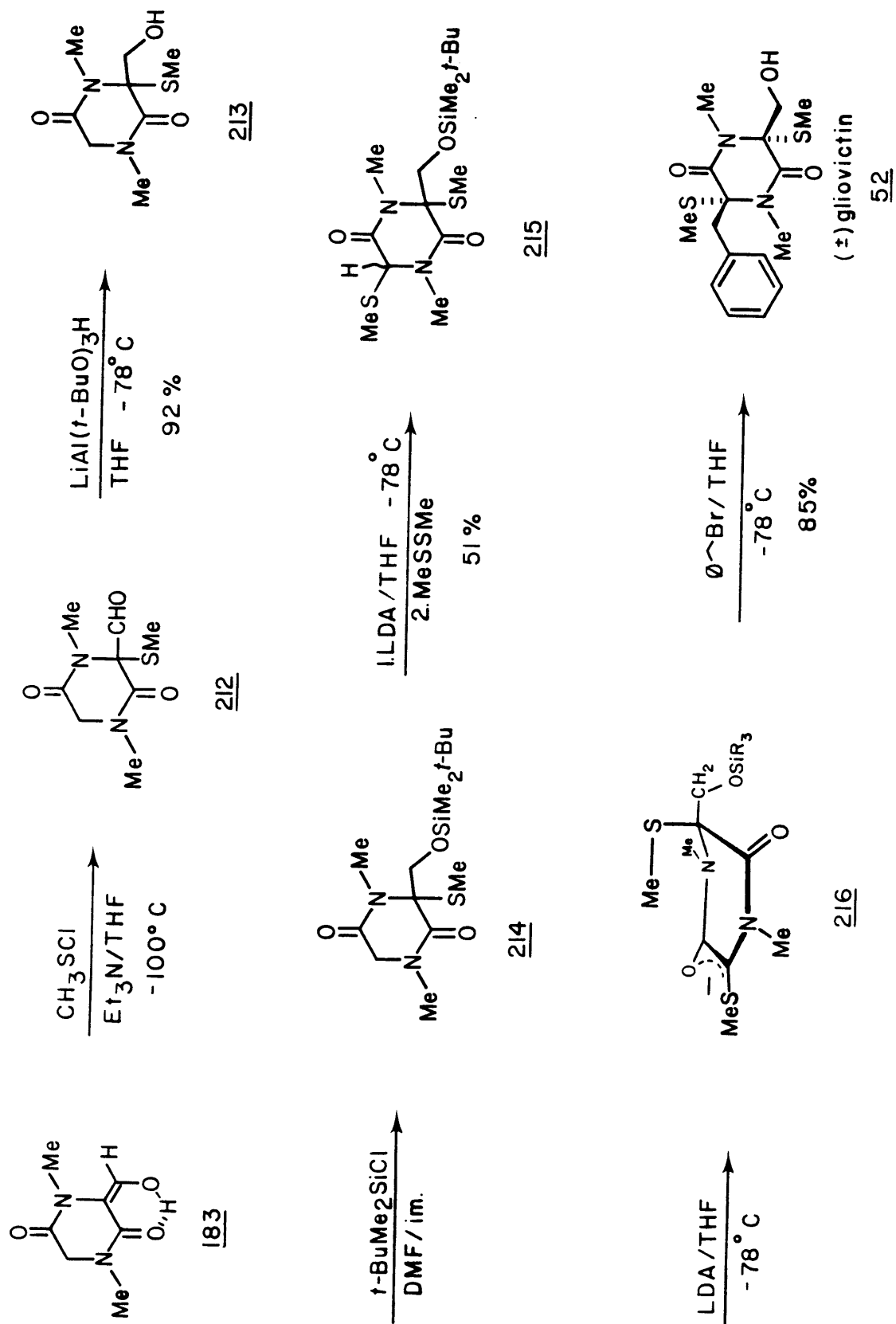
However, reaction of the potassium salt derived from **183** with *t*-butyldiphenylsilyl chloride cleanly afforded the crystalline silyl enol ether **211** in 87% yield (SCHEME 34). Deprotection of the silyl group was achieved with either, 1 equivalent of potassium fluoride in methanol at 0°C; 1 equivalent tetra-*n*-butylammonium fluoride; liquid ammonia in THF at -78°C, or mild acid hydrolysis (5% HCl in methanol for 12 hours).

Before proceeding with the introduction of thiol (and ultimately, disulfide) functionalities into the silyl protected piperazinediones, attention was diverted to a synthesis of (+)-gliovictin (52) via direct introduction of thiomethyl functionalities. As shown in SCHEME 35, sulfenylation of 183 with methylsulfenyl chloride<sup>124,125</sup> in THF at -100°C afforded the crystalline methylthio carboxaldehyde 212. Reduction of 212 with lithium tri-*t*-butoxyaluminum hydride in THF at -78°C afforded the pure, crystalline alcohol 213 in 92% yield. The alcohol was cleanly protected as its *tert*-butyldimethylsilyl ether 214 (quantitative) in the standard manner.<sup>126</sup> Stereoselective conversion of 214 to (+)-gliovictin (52), was achieved by introduction of the remaining thiomethyl and benzyl groups. Thus, sulfenylation of the enolate of 214 with methyl disulfide gave after chromatography, a mixture of diastereomers 215 in 51% yield (66% based on recovered 213). Benzylation of the enolate of diastereomers 215, followed by acidic hydrolysis of the silyl protecting group and chromatography afforded (+)-gliovictin (52) in 85% yield (38% overall from sarcosine anhydride; or 50% overall based on recovered 214). Synthetic gliovictin was indistinguishable from natural material<sup>127</sup> by <sup>1</sup>H NMR, IR, MS, TLC and combustion analysis.

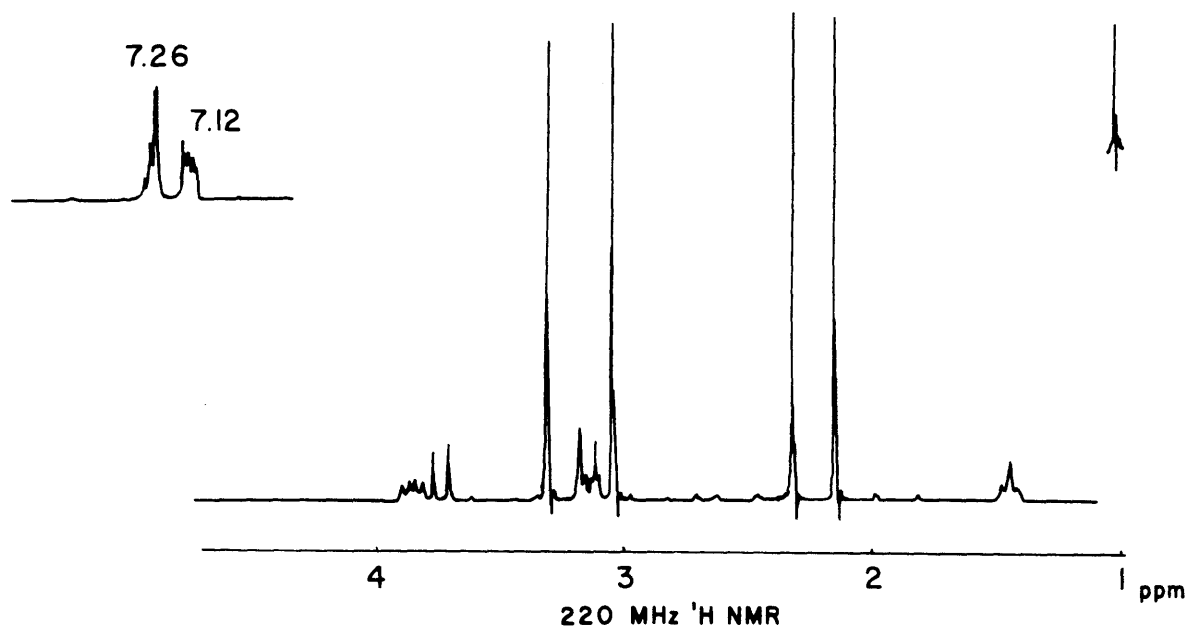
Analysis of crude gliovictin (52) by HPLC revealed that less than 10% of diastereomeric material (see 221, SCHEME 36) was formed in the benzylation step (215→52). Inspection of



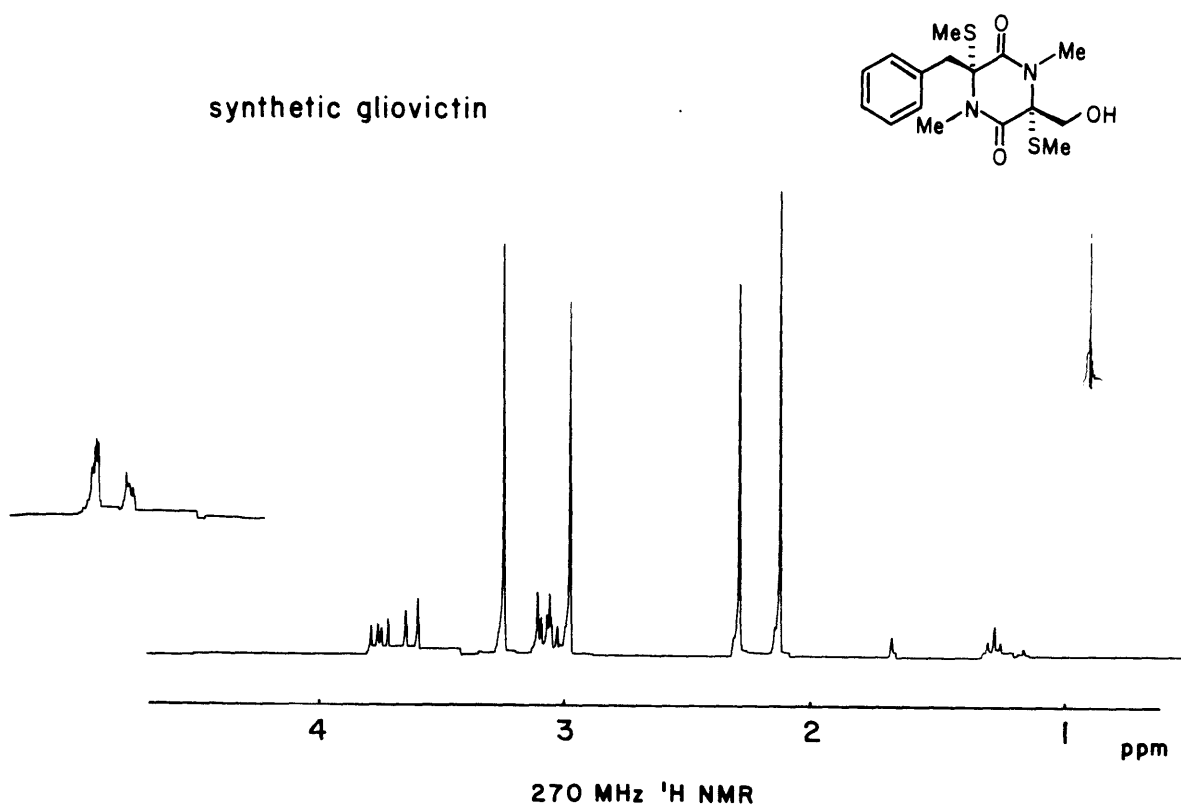
SCHEME 35



natural gliovictin



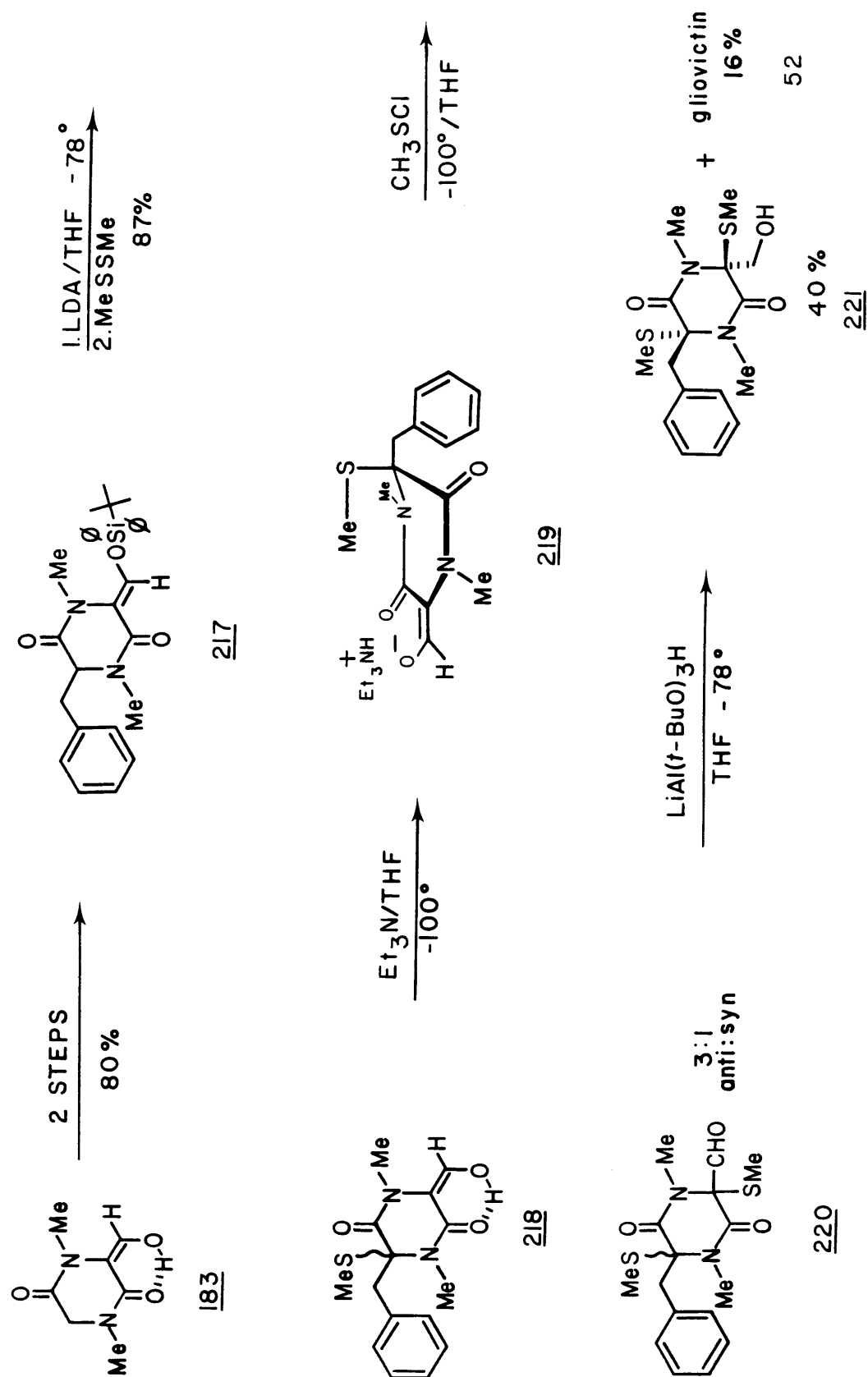
synthetic gliovictin

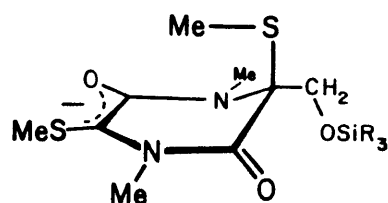


Dreiding or CPK molecular models of the enolate 216 indicates a preference for the conformation in which the bulky tert-butyldimethylsilyl group is held in a pseudoequatorial position and the methylthio group remains pseudoaxial. As shown in structure 216, the pseudoaxially disposed methylthio group can thereby shield one face of the enolate from electrophillic attack.<sup>128</sup>

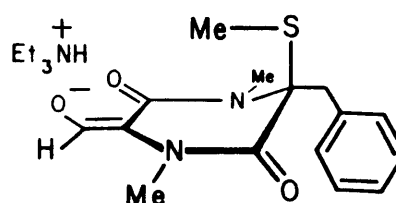
In an alternative approach (SCHEME 36), silyl enol ether 211 was benzylated to afford 217 in 92% yield. Sulfenylation of the enolate of 217 with methyl disulfide directly afforded methylthio enol ether 218 in 87% yield. An interesting in situ deprotection of the silyl group by the lithium thiomethoxide generated during sulfenylation occurred in this reaction. As evidence, chromatographic purification of 218 also afforded 85% of tert-butyldiphenylsilyl methylthio ether. Sulfenylation of the triethylammonium enolate of 218 with methylsulfenyl chloride in THF at -100°C afforded a 3:1 mixture of diastereomers 220 favoring the anti isomer. Without purification, the mixture of 220 was reduced with lithium tri-*t*-butoxy aluminum hydride in THF at -78°C to afford, after chromatography, 16% of (+)-gliovictin (52) and 40% of the diastereomer 221 (epi-gliovictin). The preponderance of diastereomer 221 produced in this sulfenylation/reduction sequence (SCHEME 36, 218→220→221) may again reflect the shielding effect of a pseudoaxially disposed thiomethyl group during sulfenylation (cf.219 and 216). In both the case of 219 and of 216 the electrophile is reacting

SCHEME 36





216



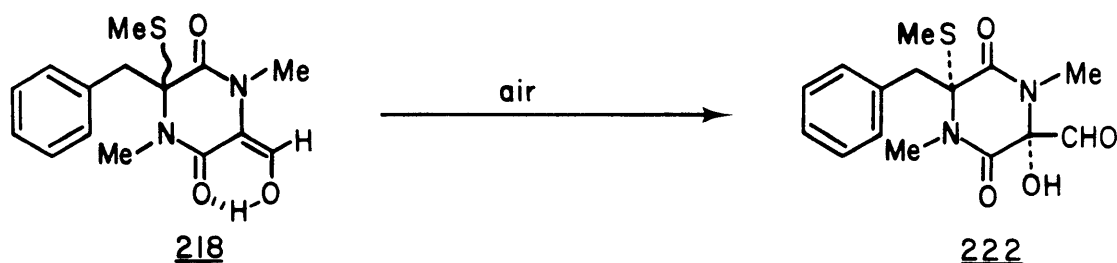
219

93

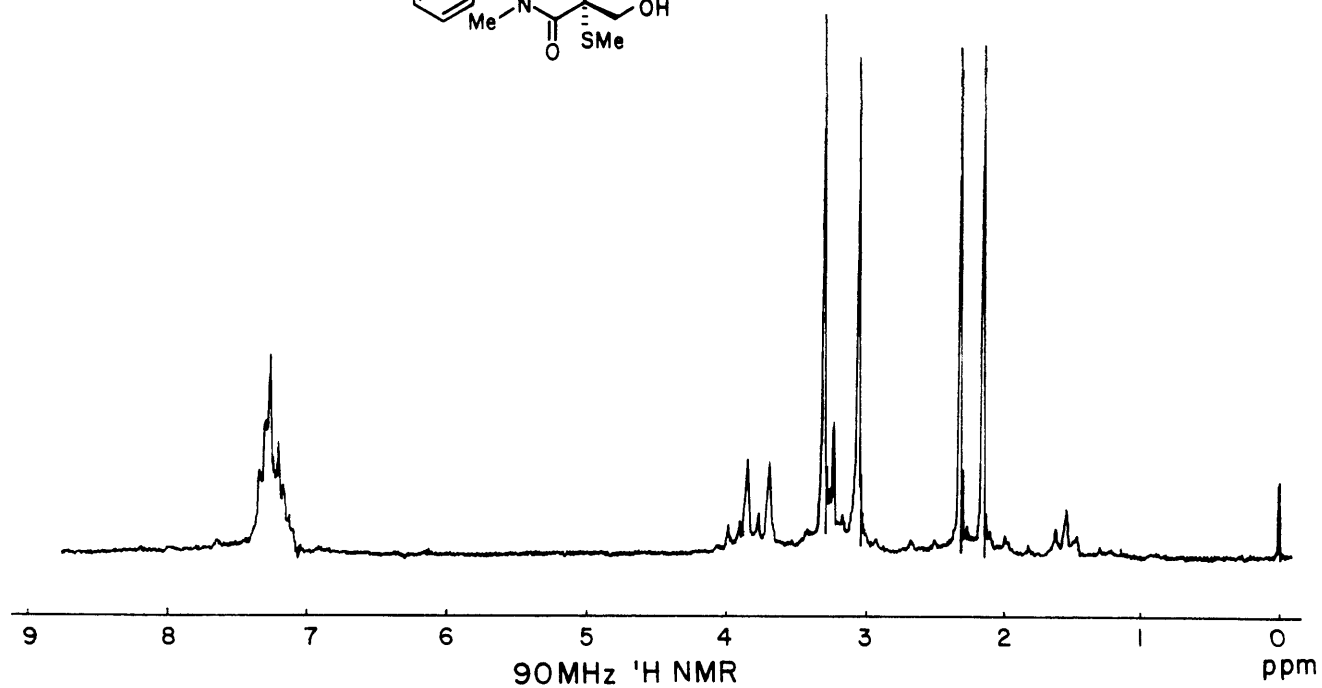
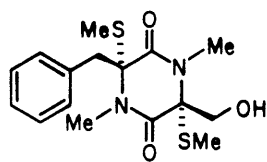
preferentially on the face opposite to the thio methyl group. This interesting phenomenon will be discussed again later.

The  $^1\text{H}$  NMR spectra of (+)-gliovictin (52) and the diastereomer epi-gliovictin (221) are illustrated. It is interesting to note the anisotropic shielding effect of the aromatic ring on the O-H proton of gliovictin (52) and on the methyl thio group across the ring in epi-gliovictin (221).

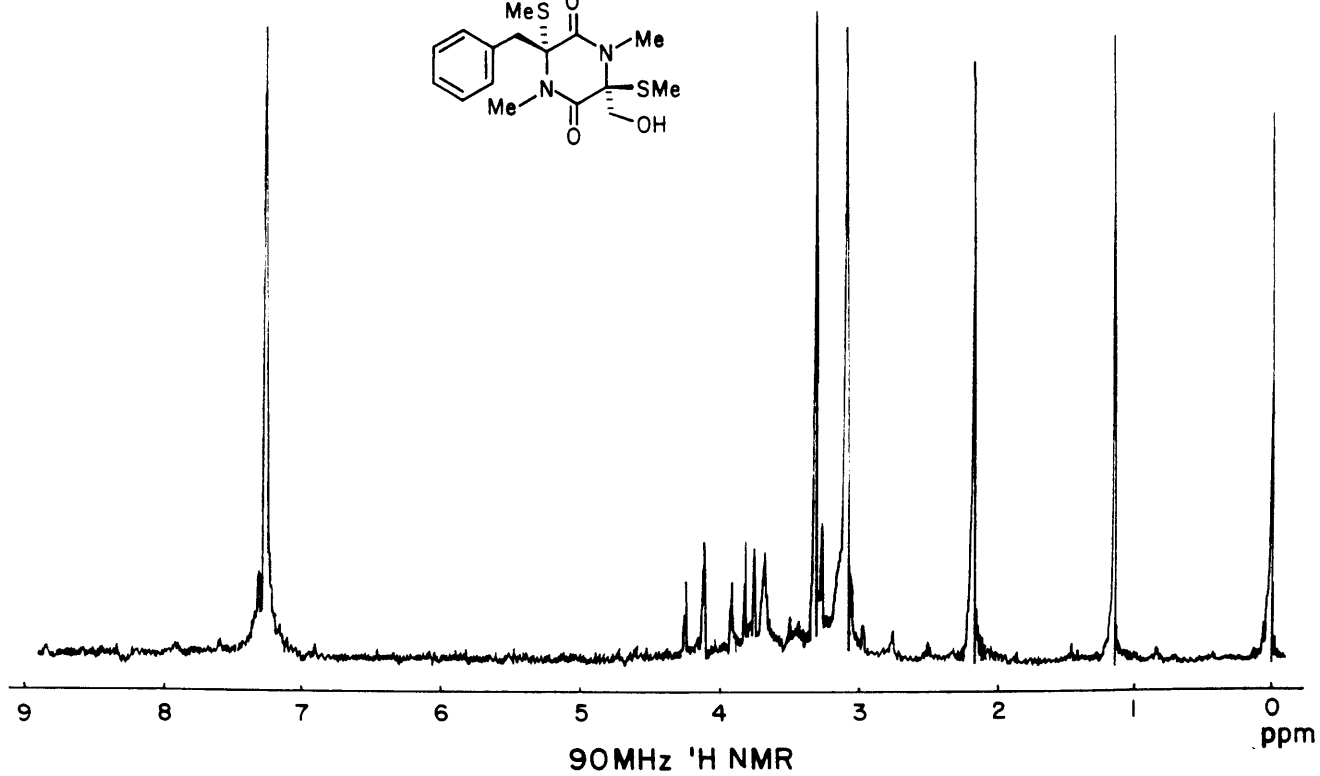
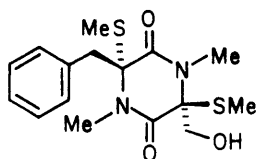
It was interesting to observe that sulfide 218 was extremely air sensitive and had to be used immediately after its preparation. Exposure of oily 218 (neat) to the atmosphere for 12 hours resulted in the precipitation of a crystalline  $\alpha$ -hydroxycarboxaldehyde identified as 222 (syn isomer).



Other, unidentified decomposition products were also formed along with 222. The unusual sensitivity of 218 to oxygen was



## EPI-GLIOVICTIN



particularly surprising, since 183, 223, 246 and 249 were all found to be stable to the atmosphere and required no special handling.

A third approach to the gliovictins was attempted without success and is shown in SCHEME 37. Benzylation of 214 afforded 226 in 77% yield. An efficient, yet lengthier preparation of 226 was also achieved from 217 (SCHEME 37). When 226 was treated with LDA and methyl disulfide, the expected gliovictin products (221 or 52) were not obtained. Instead, a single crystalline product (227) was obtained that was devoid of both methylthio and silyl groups. Mass spectral data on 227 indicated a dimeric structure ( $C_{28}H_{30}N_4O_4$ ). A rigorous structural assignment for 227, however, was not made. It is interesting to compare the reaction of 214 (SCHEME 35) and 226 (SCHEME 37) with LDA and methyl disulfide; 214 affords the expected sulfenylated products (215); 226, in contrast, follows an entirely different path. The reasons for this anomaly are not entirely understood but dramatically illustrates how a change in molecular environment can completely alter the course of a seemingly simple and straightforward procedure.

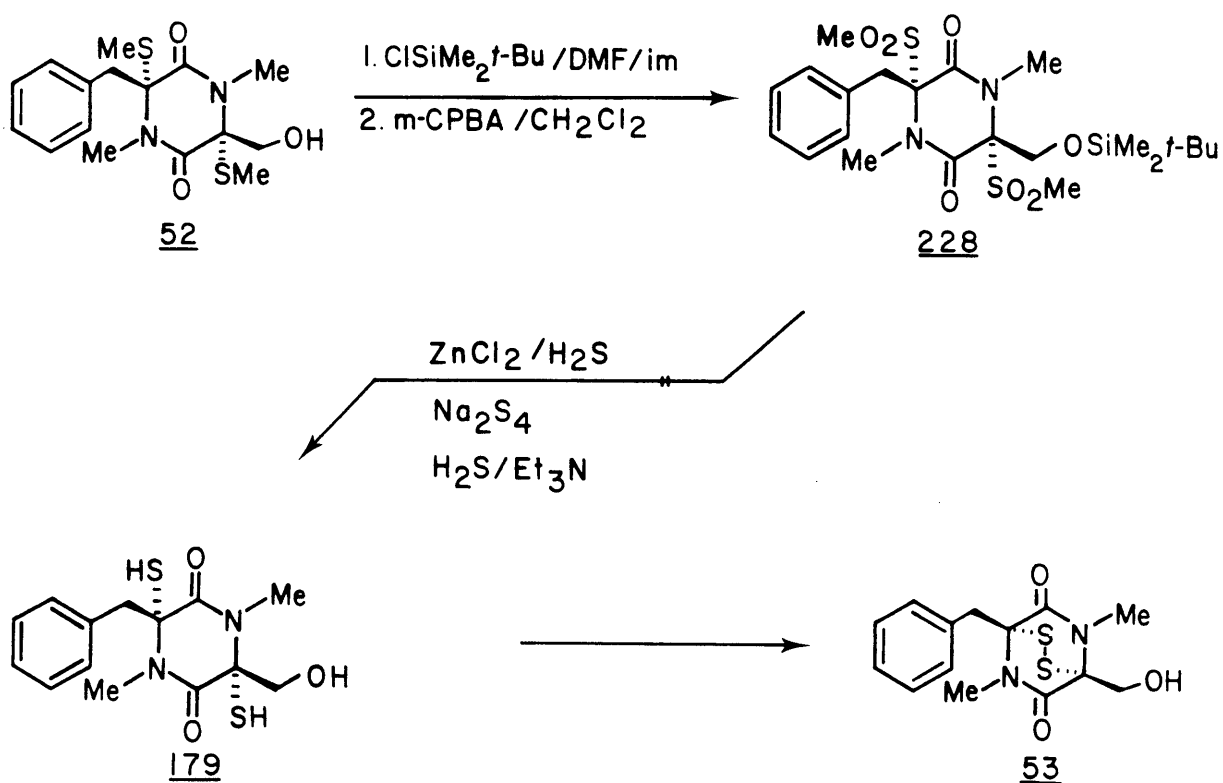
The efficient preparation of (+)-gliovictin (SCHEME 35) prompted attempts to transform the methyl thio groups into mercapto groups and thus into hyalodendrin. As mentioned earlier, Schmidt was able to transform the bisethylsulfone (101, SCHEME 10) into the corresponding epitetrasulfide (99).<sup>64</sup>



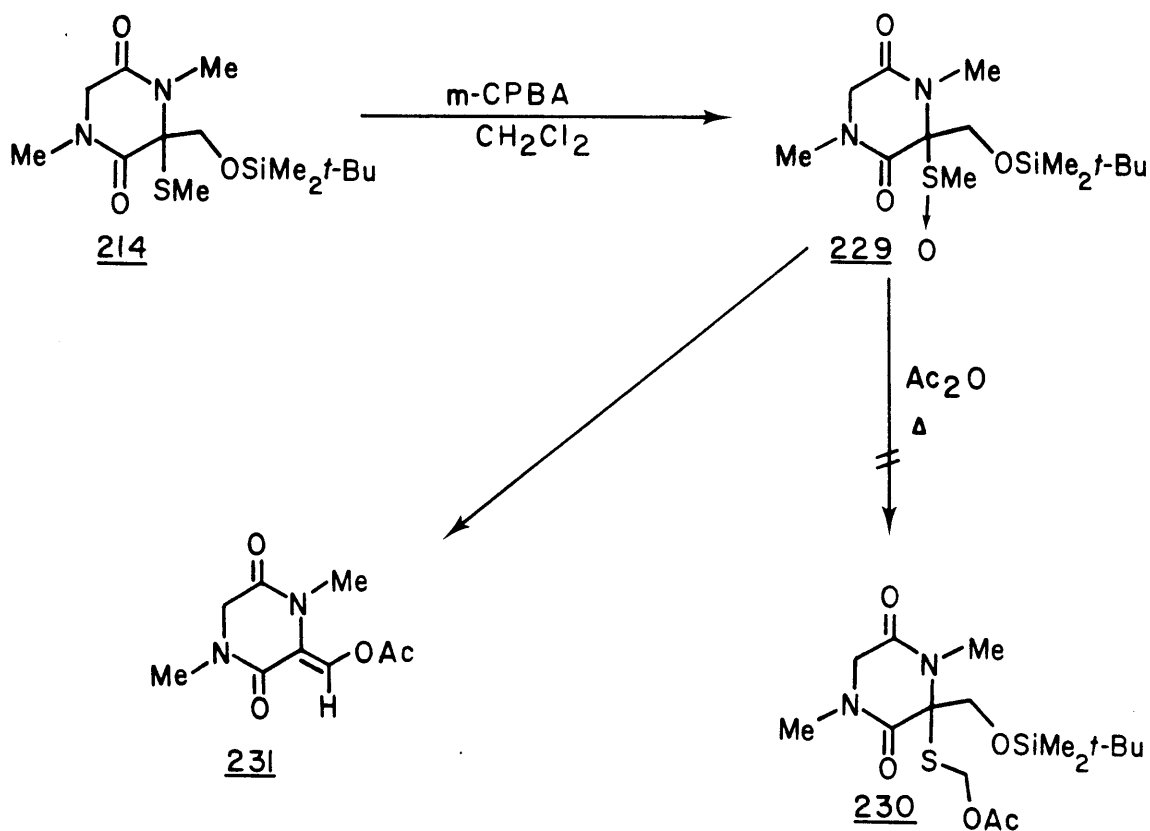


Thus, the bismethylsulfone (228) was prepared from gliovictin in two steps (SCHEME 38). Unfortunately, 228 was inert to sodium tetrasulfide in refluxing chloroform;  $\text{H}_2\text{S}/\text{Et}_3\text{N}$ ; and  $\text{H}_2\text{S}/\text{ZnCl}_2$ . Therefore, the Schmidt procedure may be applicable only to 3,6-unsubstituted sulfones (i.e., 101).

SCHEME 38



In another attempt to transform gliovictin into hyalodendrin, it was thought that Pummerer rearrangement of the methylsulfoxide (i.e., 229) might provide hemithioacetal (i.e., 230) which could be hydrolyzed to the mercaptan. In the model study (SCHEME 39, however, sulfoxide 229 when heated in acetic anhydride underwent an interesting desulfurization to afford enolacetate 231 (quant.); none of the

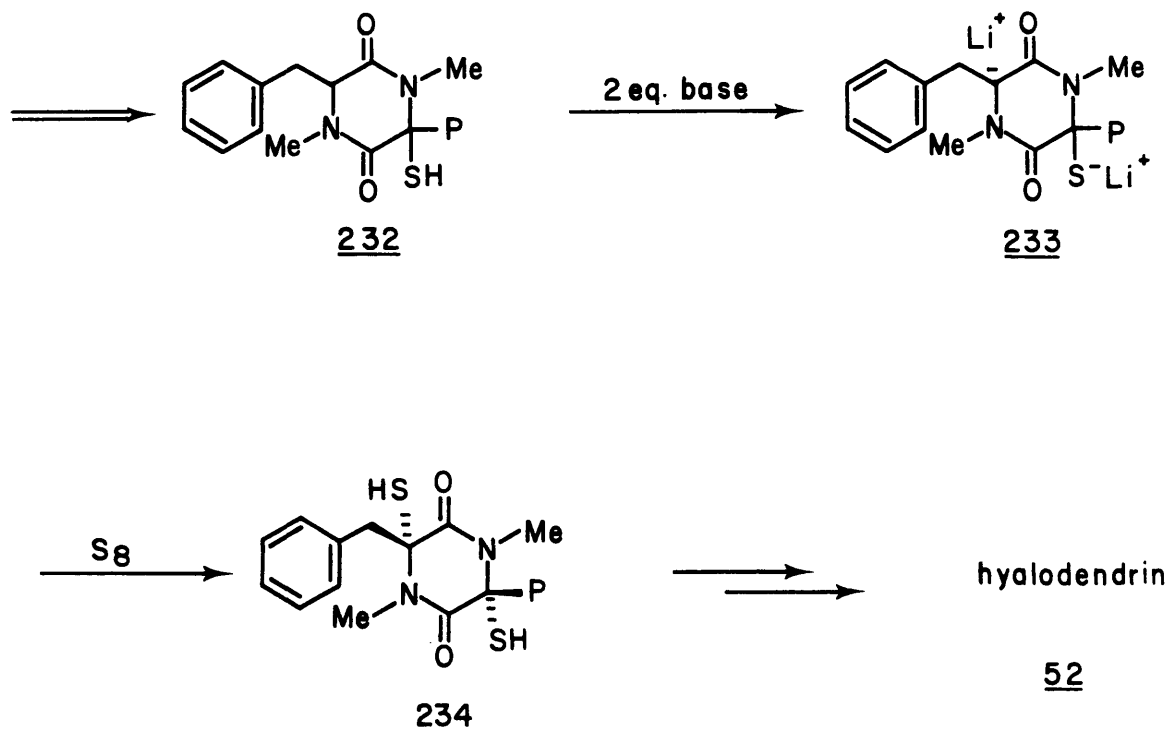


desired hemithioacetal **230** was observed. The observed  $\beta$ -elimination rather than the desired  $\alpha$ -elimination ("normal Pummerer") has precedence in the  $\beta$ -lactam field.<sup>129</sup>

During the course of the investigation illustrated in SCHEME 37, an alternative approach to hyalodendrin was formulated (SCHEME 40). Introduction of sulfur at the formyl position followed by protection of the carboxaldehyde or hydroxymethyl group affords intermediate **232**. Subsequent Schmidt-type sulfenylation of dianion **233** is envisioned to produce cis-dimercaptan **234**. Removal of the protecting group (P) and oxidation to the disulfide would give hyalodendrin.

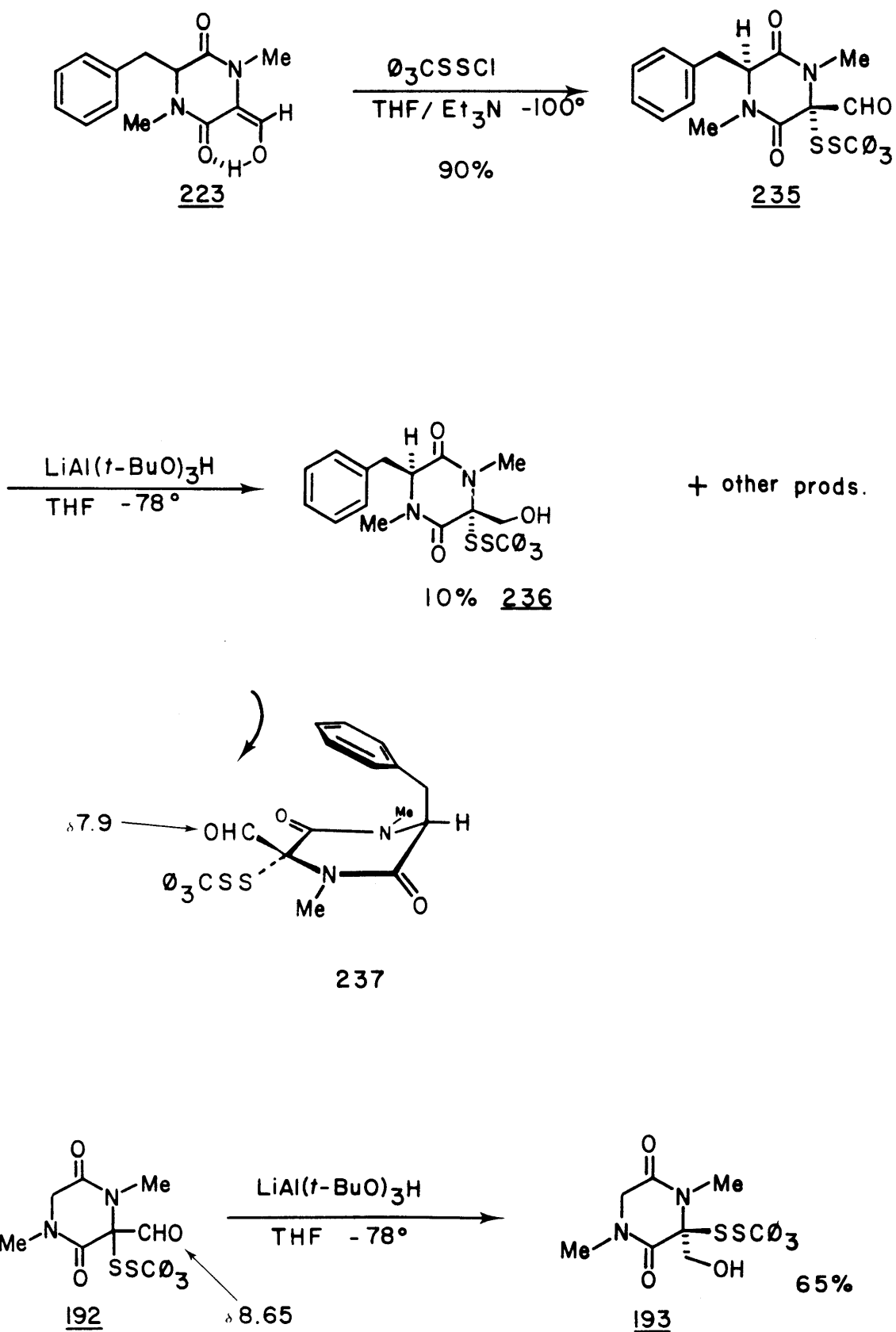
# Strategy

## SCHEME 40



Toward this end, 223 was sulfenylated with triphenylmethyl chlorodisulfide to afford syn-disulfide 235 (>10:1, syn:anti) in high yield. Selective reduction of 235 was not realized when treated with lithium tri-*t*-butoxyaluminum hydride in THF at low temperature. A small amount (10%) of the desired disulfide alcohol (236) was obtained along with other products resulting from competitive reduction of the disulfide and carboxaldehyde (SCHEME 41). This poor selectivity is in marked contrast to the analagous reduction on 192 (cf. SCHEME 29 and 41). This anomaly may be explained by steric crowding of the carboxaldehyde by the benzyl group (see 237) and thus hindering approach of the reducing reagent. This interaction is supported by comparing the  $^1\text{H}$  NMR spectra of 192 and 235: the aldehyde proton of 192 appears at 8.65,

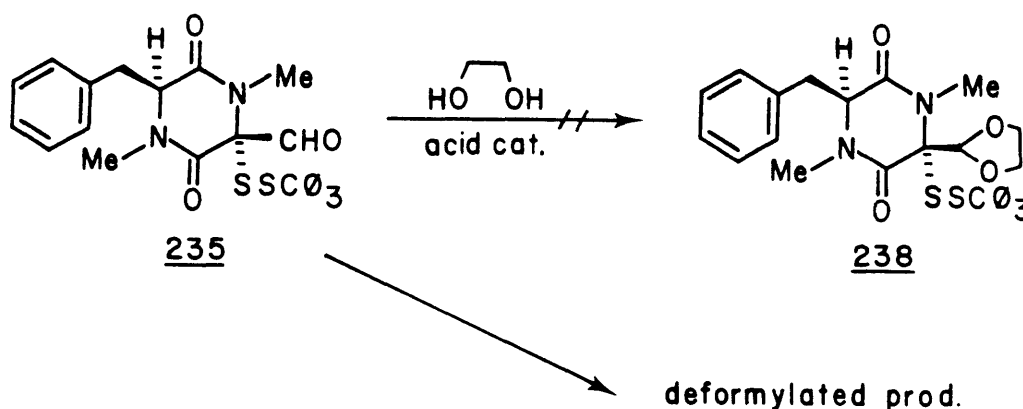
## SCHEME 41



whereas the aldehyde proton of 235 appears upfield at  $\delta 7.9$  owing to the anisotropic shielding effect of the aromatic ring.

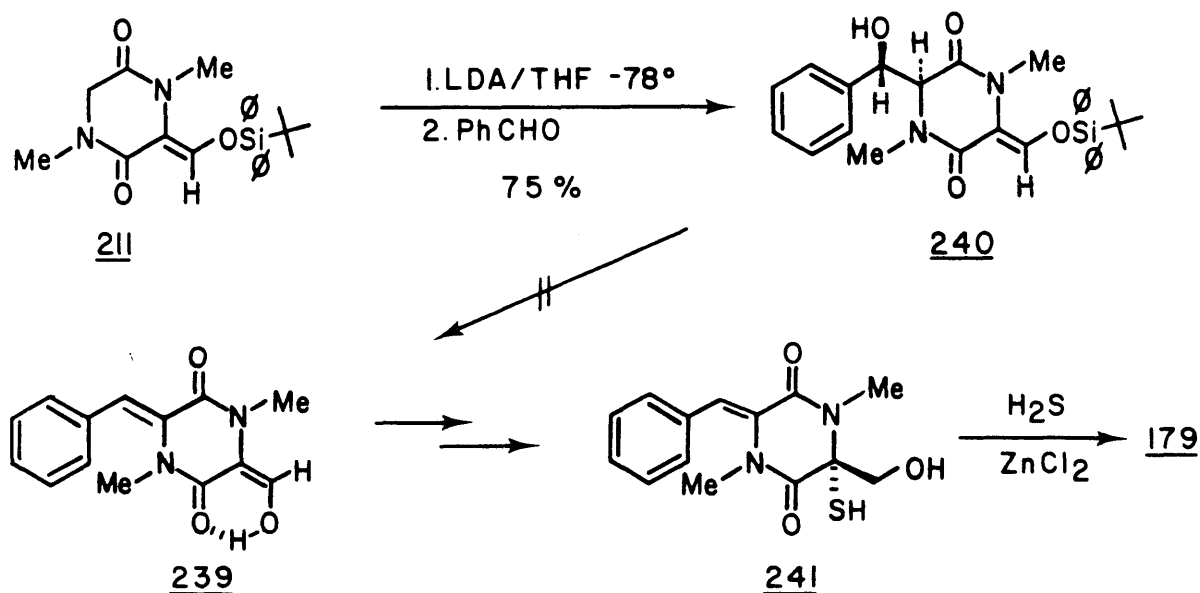
Attempted protection of the carboxaldehyde of 235 as the acetal 238 led only to the deformylated product under a variety of conditions (SCHEME 42).

SCHEME 42

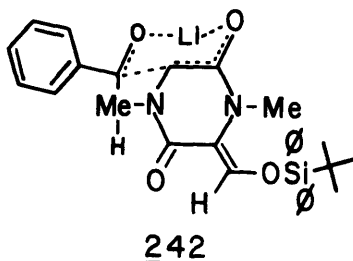


Related to the strategy of SCHEME 40, an attempt was made to prepare formyl olefin 239 by dehydration of the

SCHEME 43



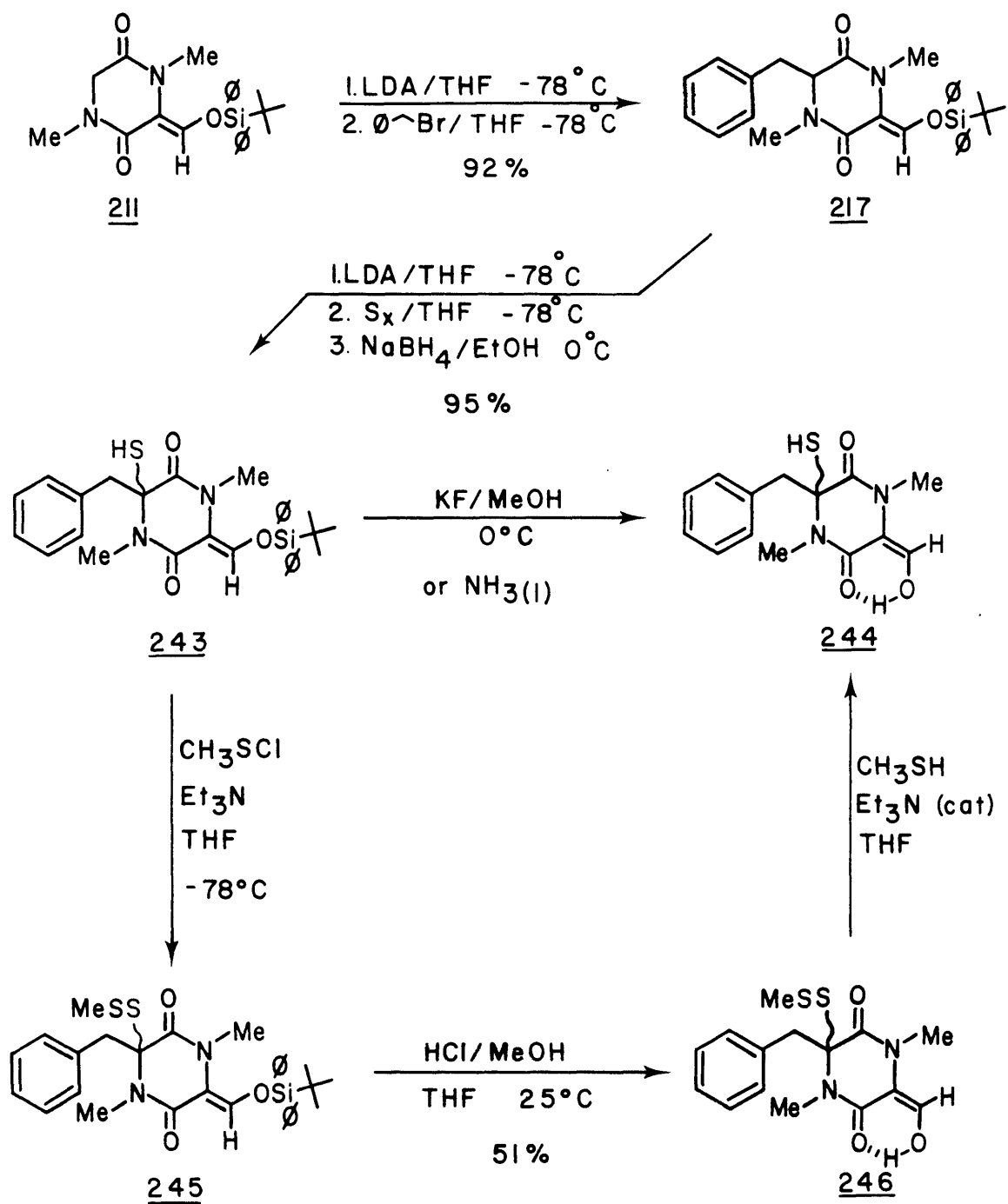
benzyl carbinol of 240. It was thought that sulfenylation of 239 followed by reduction to mercapto alcohol 241 and subsequent  $\text{H}_2\text{S}/\text{ZnCl}_2$  addition according to Ottenheijm<sup>72-74</sup> would provide dithiol 179. Although dehydration of 240 was not achieved, it was of interest that the reaction of the enolate derived from 211 with benzaldehyde afforded a single, crystalline alcohol 240 in 75% yield. Consideration of the spectral data, and related recent work by Heathcock<sup>130</sup> suggest that the stereochemistry of 240 (shown in SCHEME 43) is governed by a transition state in which the bulky tert-butyldiphenylsilyl residue and aromatic ring of benzaldehyde orient away from each other in a  $\text{Li}^+$  chelated chair conformation (i.e., 242).



Further investigations according to the strategy of SCHEME 40 and that mentioned above, were not pursued.

Thus far, the silyl protecting group had performed admirably. Virtually all the compounds containing the tert-butyldiphenylsilyl group were crystalline and required no chromatographic purification. Furthermore, this protecting group permitted reactions under strongly basic conditions and was readily removed under a variety of conditions to afford the desired enolic compounds (i.e., 218 and 223). However, there remained one problem; namely, as pointed out in SCHEME 34, the tert-butyldiphenylsilyl group is readily cleaved by liquid ammonia in THF at  $-78^{\circ}\text{C}$ . Consequently, sulfenylation of 217 with elemental sulfur in liquid ammonia is no longer possible. Elemental sulfur is very soluble in liquid ammonia (38% at  $-78^{\circ}\text{C}$ ) and permits nearly homogeneous sulfenylations (i.e., 102→160, 204→205, 208→209). Orthorhombic sulfur ( $\text{S}_8$ ) is relatively insoluble in solvents such as ether, THF, dioxane and DME. Attempted sulfenylation of 102 and 217 in THF afforded dark and complex mixtures of products. A very simple solution to this problem was discovered quite by coincidence. During an attempted sulfenylation of 217 on a moist day, the elemental sulfur was weighed into the reaction vessel and then gently warmed with a heat gun under vacuum to insure that the flask and the sulfur were dry. Surprisingly, addition of THF to the "toasted" sulfur at room temperature resulted in complete dissolution ( $\sim 0.50\text{g}$  in  $50\text{mL}$ ). Apparently, upon gentle warming, the rhombic sulfur undergoes an allotropic conversion to monoclinic sulfur which is a more soluble crystalline form of

## SCHEME 44

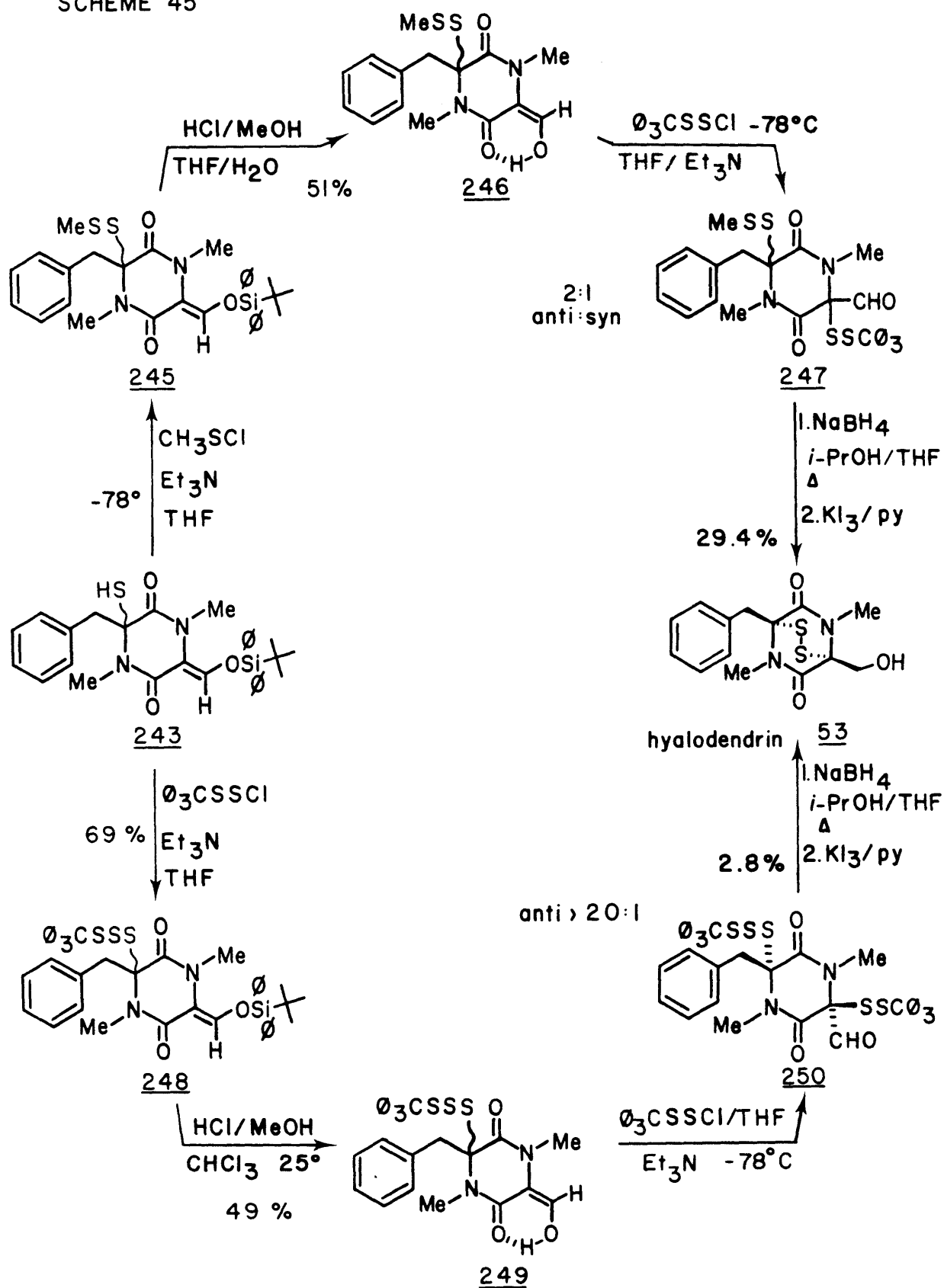




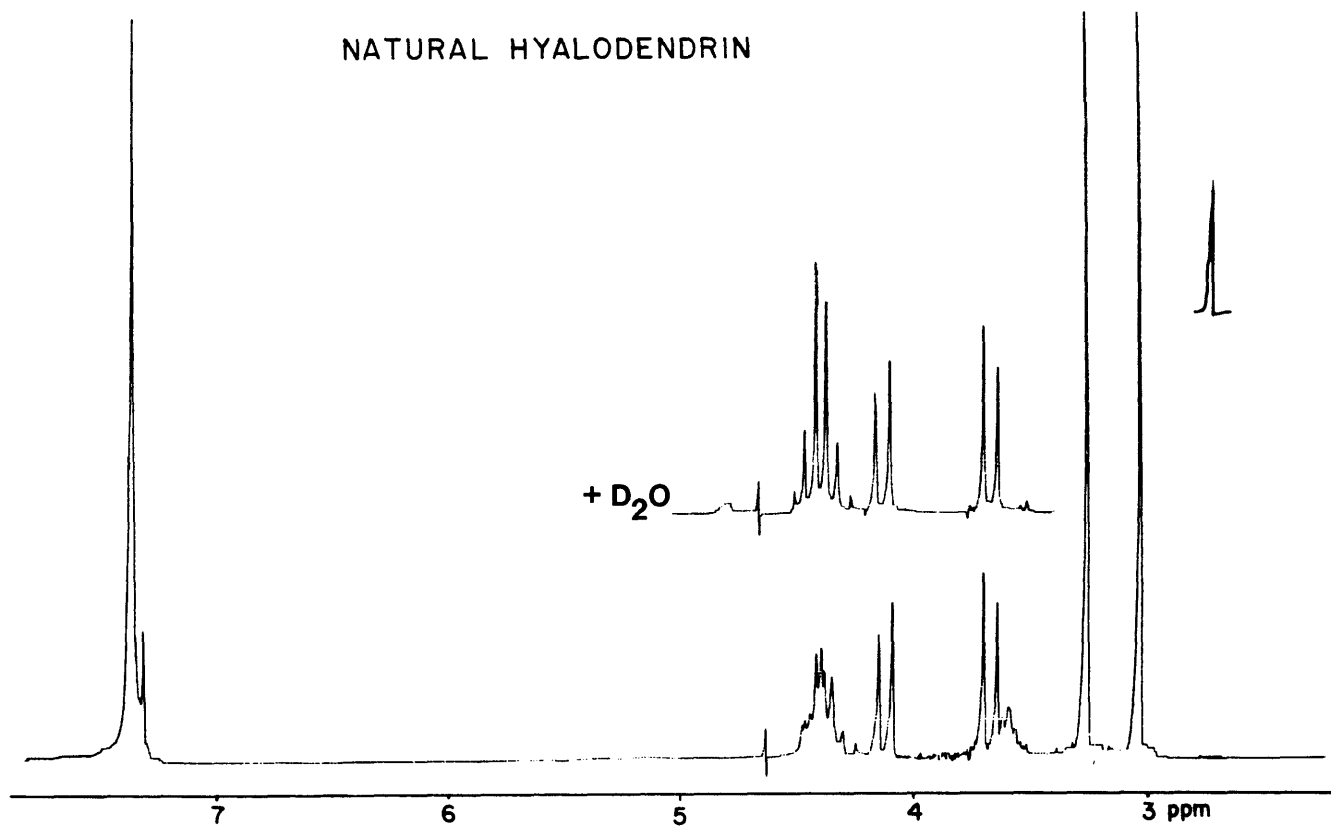
sulfur. Thus, reaction of 217 with 2 equiv of sulfur in THF at  $-78^{\circ}\text{C}$  followed by a reductive workup, afforded pure thiol 243 as a brittle, white foam in nearly quantitative yield (SCHEME 44). Deprotection of 243 with either 1.0 equiv of KF in MeOH, or exposure to liquid ammonia led to the production of a highly insoluble white solid which ran as a single spot on TLC. This material would not dissolve in THF,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ ,  $\text{Et}_2\text{O}$ , MeOH, EtOAc, EtOH, DME, dioxane or water. The  $^1\text{H}$  NMR spectrum of this substance in DMSO  $d_6$  was complex and certainly not consistent with structure 244. Suspecting anomalous behavior, thiol 243 was converted into the corresponding methyl disulfide 245, and the silyl group removed by mild acid hydrolysis to afford the enolic disulfide 246. Reduction of the disulfide with excess methane thiol with a catalytic amount of triethylamine led cleanly to the production of a substance identical to that obtained by deprotection of 243. The identity of this substance was not elucidated until some time after the experiments described above were performed. In the meantime, sulfenylations of S-protected enol compounds (i.e., 246) were investigated.

As shown in SCHEME 45, sulfenylation of 246 with triphenylmethyl chlorodisulfide afforded a 2:1 mixture of diastereomers 247 favoring the undesired anti isomer. Reduction of 247 with sodium borohydride followed by oxidation with a 2.5% solution of  $\text{KI}_3$  in pyridine<sup>72-74</sup> at  $0^{\circ}\text{C}$  and chromatography on silica gel afforded a 29.4% yield of (+)-hyalodendrin as pale

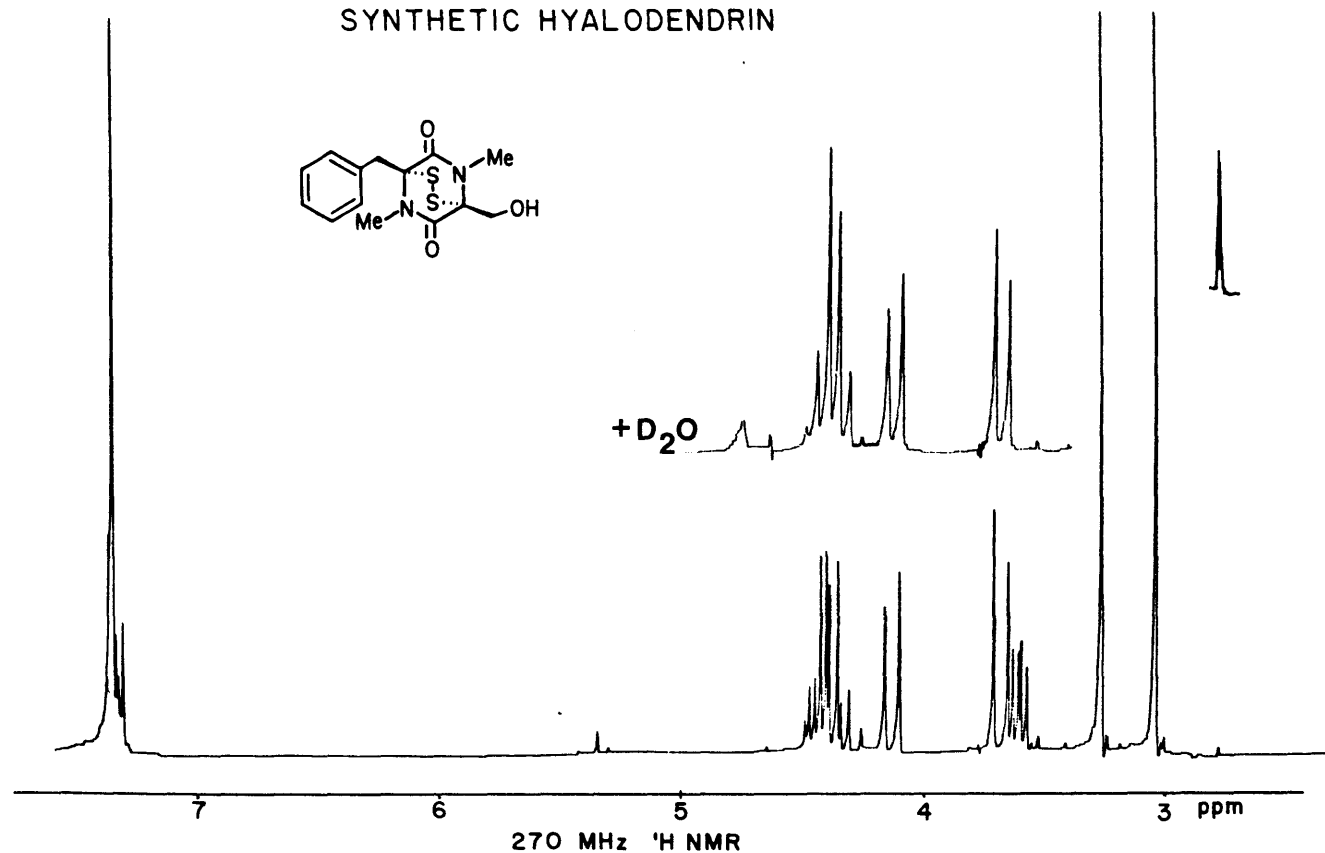
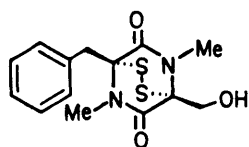
SCHEME 45



## NATURAL HYALODENDRIN



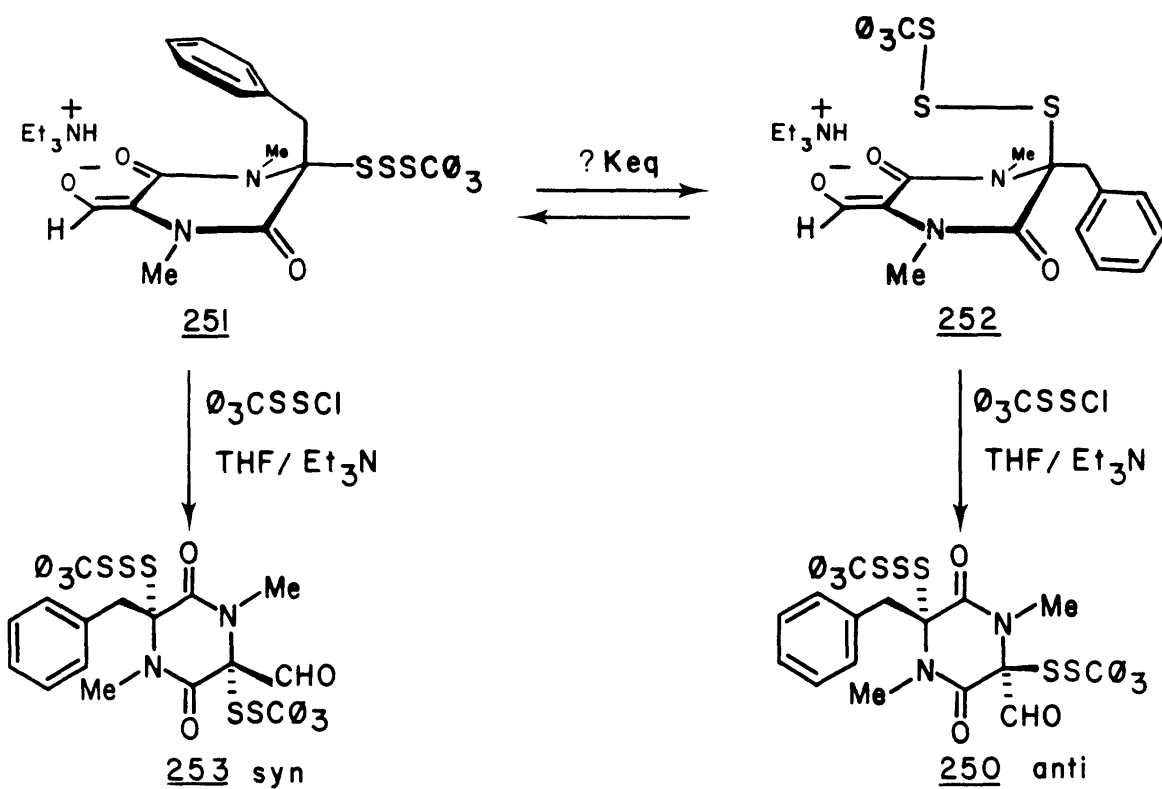
## SYNTHETIC HYALODENDRIN



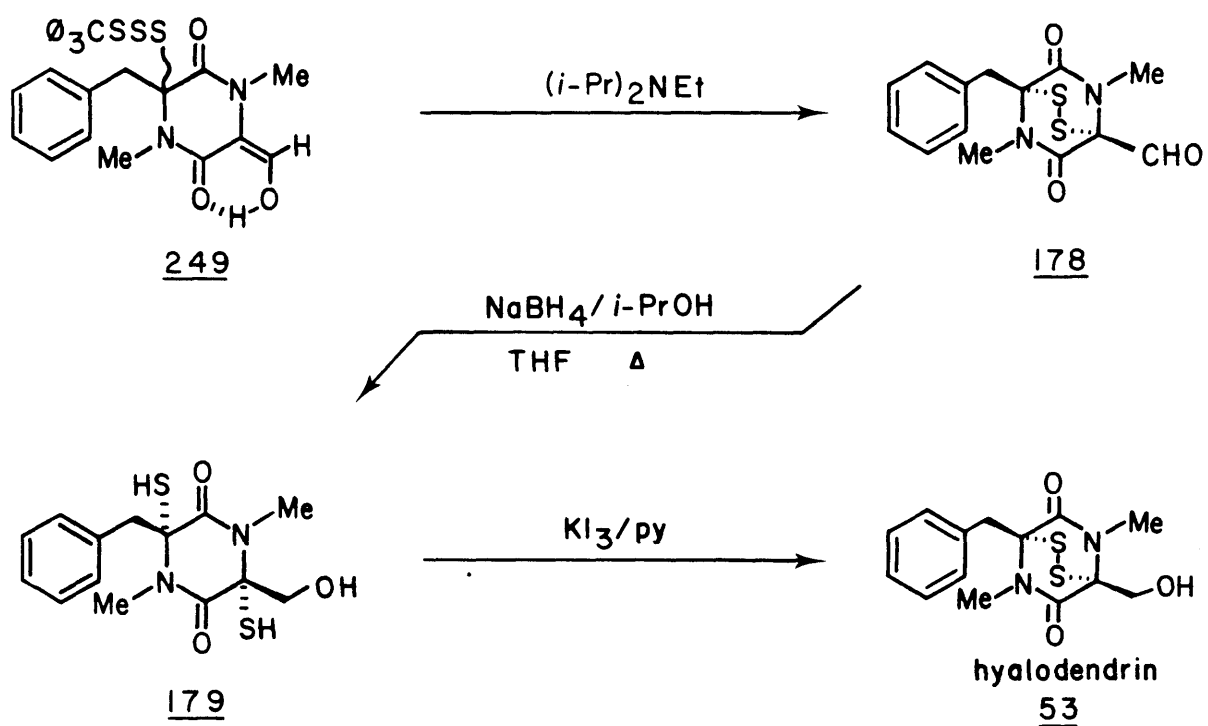
yellow crystals. The synthetic hyalodendrin was identical to natural material<sup>127</sup> by  $^1\text{H}$  NMR, IR, MS and TLC. Although the stereoselectivity of the sulfenylation was low (i.e., 246→247), the overall chemical yield (11%) from sarcosine anhydride is superior to that of Strunz<sup>106</sup> (1-2% overall from sarcosine anhydride) and Kishi<sup>59,104</sup> (6% overall from sarcosine anhydride, see SCHEME 21).

In an effort to reverse the preference for sulfenylation on the face opposite to the sulfur functionalities, the bulky triphenylmethyl trisulfide group was introduced at the 6-position. Thus, thiol 243 was converted into the corresponding trityl trisulfide 248 by reaction with triphenylmethyl chlorodisulfide. Hydrolysis of the silyl group afforded enolic trisulfide 249. Based on the stereocontrol observed in the syntheses of gliovictin (see SCHEME 35 and 36), it was hoped that the bulky trityl trisulfide would assume a pseudoequatorial position, forcing the benzyl group to be pseudoaxially disposed, and thus shielding the same face of the enolate during sulfenylation (see SCHEME 46, rotamer 251). In the event, sulfenylation of 249 with triphenylmethyl chlorodisulfide in the presence of triethylamine afforded a single isomer (250) which, when reduced and oxidized under the same conditions employed for 247, gave a very low yield of hyalodendrin (2.8%). From this result, it was concluded that mostly the undesired anti isomer (250) was formed and that rotamer 252 (SCHEME 46)

SCHEME 46

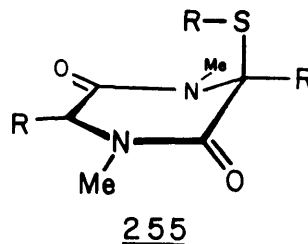
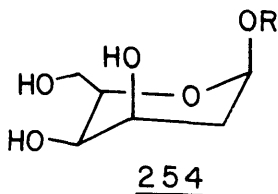


SCHEME 47



is the reacting conformer.

These results (SCHEME 45), together with consideration of the stereoselectivity of the gliovictin routes (SCHEME 35 and 36) and the results of Fukuyama and Kishi<sup>59</sup> require a reevaluation of the reasons<sup>59,131</sup> thought to govern the conformational preferences and thus stereochemical reactivities of these systems. It is quite clear that in all cases, regardless of substitution, reaction with both carbon and sulfur electrophiles occurs preferentially (albeit to varying degrees) on the face opposite to the sulfur functionality. It was thought,<sup>59,131</sup> naively perhaps, that steric factors are responsible for the conformational preferences: the bulky group assumes a pseudoequatorial position and the less bulky group, a pseudoaxial position. If this were strictly the case, rotamer 251 and not rotamer 252 (SCHEME 46) should have been predominant in the case discussed above. This, taken together with the other systems studied, seem to indicate that the sulfur atoms at the 3 or 6 positions have an electronic preference to be situated in a pseudoaxial position. This situation is analogous to the well known (but not completely understood) anomeric effect<sup>124a-d</sup> observed in carbohydrate chemistry(cf. 254 and 255)

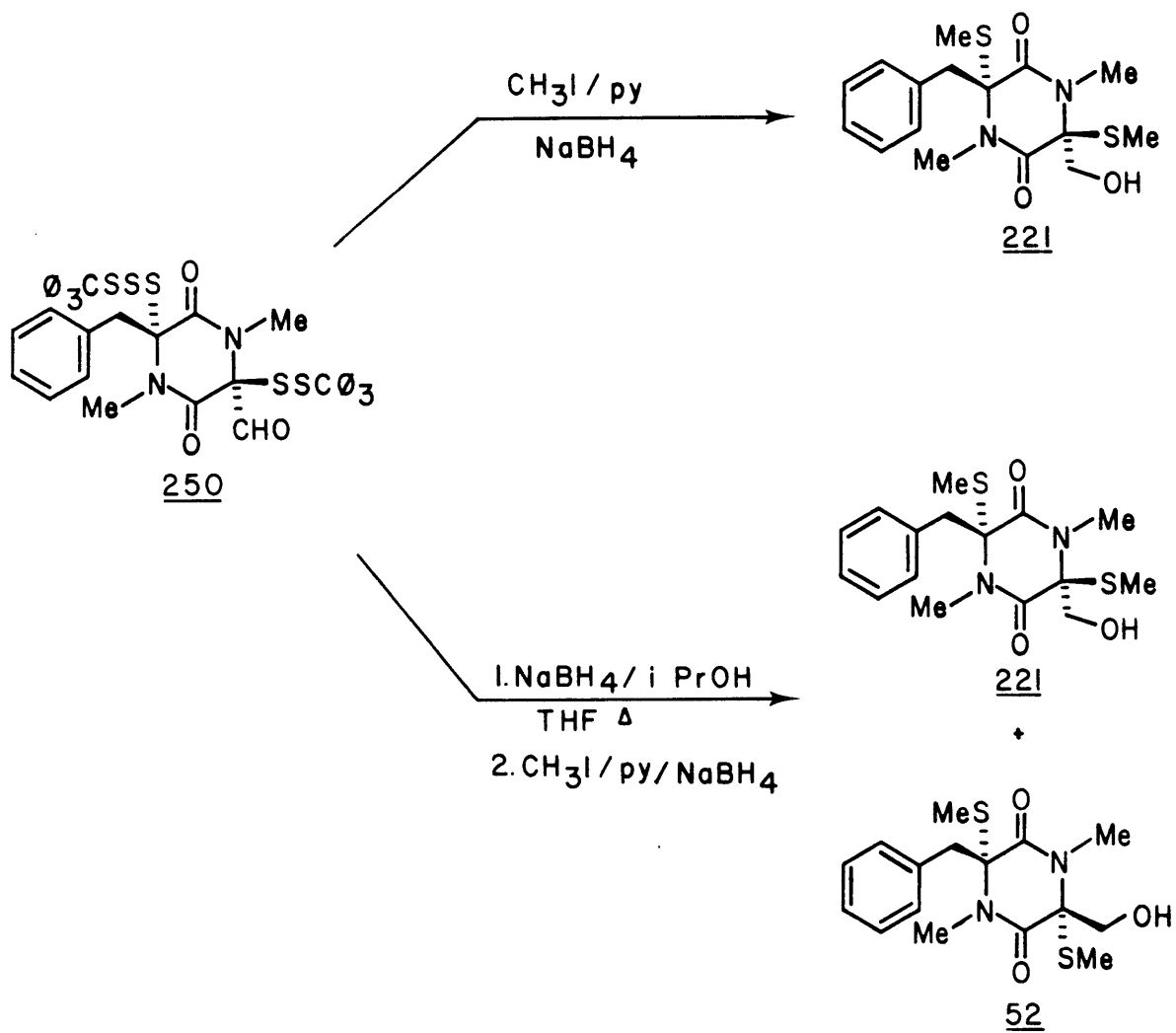


The amide nitrogen atom and sulfur atom (255) are situated geminally (hemithioaminal-like structure) much the same way the oxygen atoms of 254 are situated geminally (ketal).

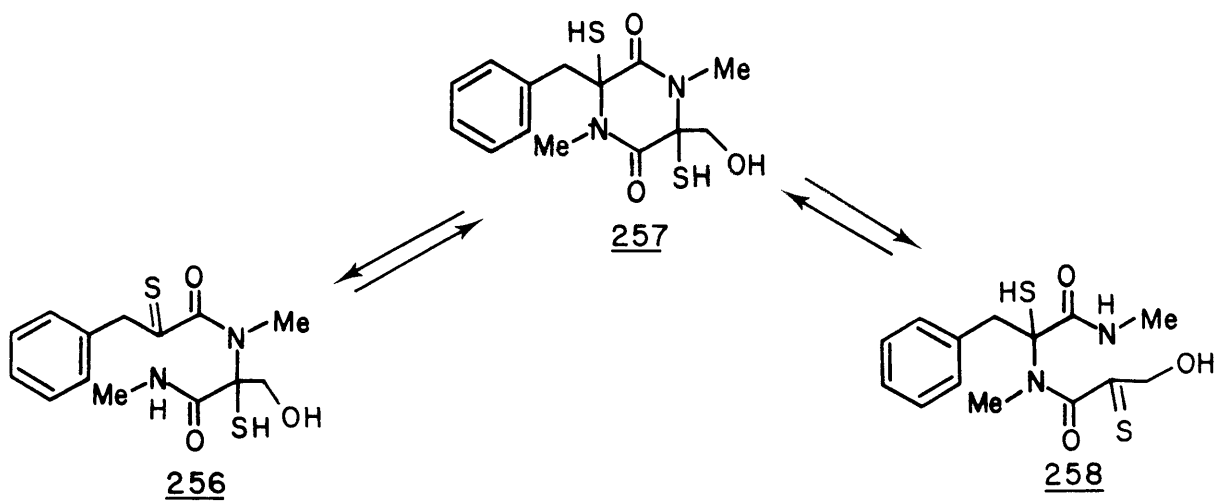
As a final check on the stereochemistry of 250, reductive methylation of 250 ( $\text{CH}_3\text{I}$ ,  $\text{NaBH}_4$ , PY) according to Strunz<sup>29</sup> produced almost exclusively (>10:1 of 221:52 by HPLC analysis) epi-gliovictin (221). Interestingly however, when 250 was first refluxed in i-PrOH/THF with excess sodium borohydride and then methylated (SCHEME 48) a 4:3 ratio of epi-gliovictin (221) and gliovictin was observed (HPLC analysis and isolation). Since it was known that only one isomer was formed in the sulfenylation (249→250), refluxing 250 with  $\text{NaBH}_4$  apparently epimerized the anti isomer to a mixture of syn and anti isomers. This observation is similar to the epimerization of an epidithiapiperazinedione to the antipodal epimonothiapiperazinedione (see SCHEME 6) and may involve equilibration of thio-carbonyl compounds 256 and 258 through dithiol 257 (cf. SCHEME 7 and 49) as proposed by Ottenheijm.<sup>53</sup>

From these observations, it seemed that rotamer 252 was indeed the predominant species. If this were so, it seemed possible that advantage of this conformational preference could be taken in bringing about the intramolecular cyclization of 249 to 178 (see SCHEME 47). In the event, treatment of 249 with DIPEA slowly consumed the starting material (two weeks, room temperature). Attempts to isolate 178 were not undertaken. Direct reduction of the reaction mixture with

SCHEME 48



SCHEME 49

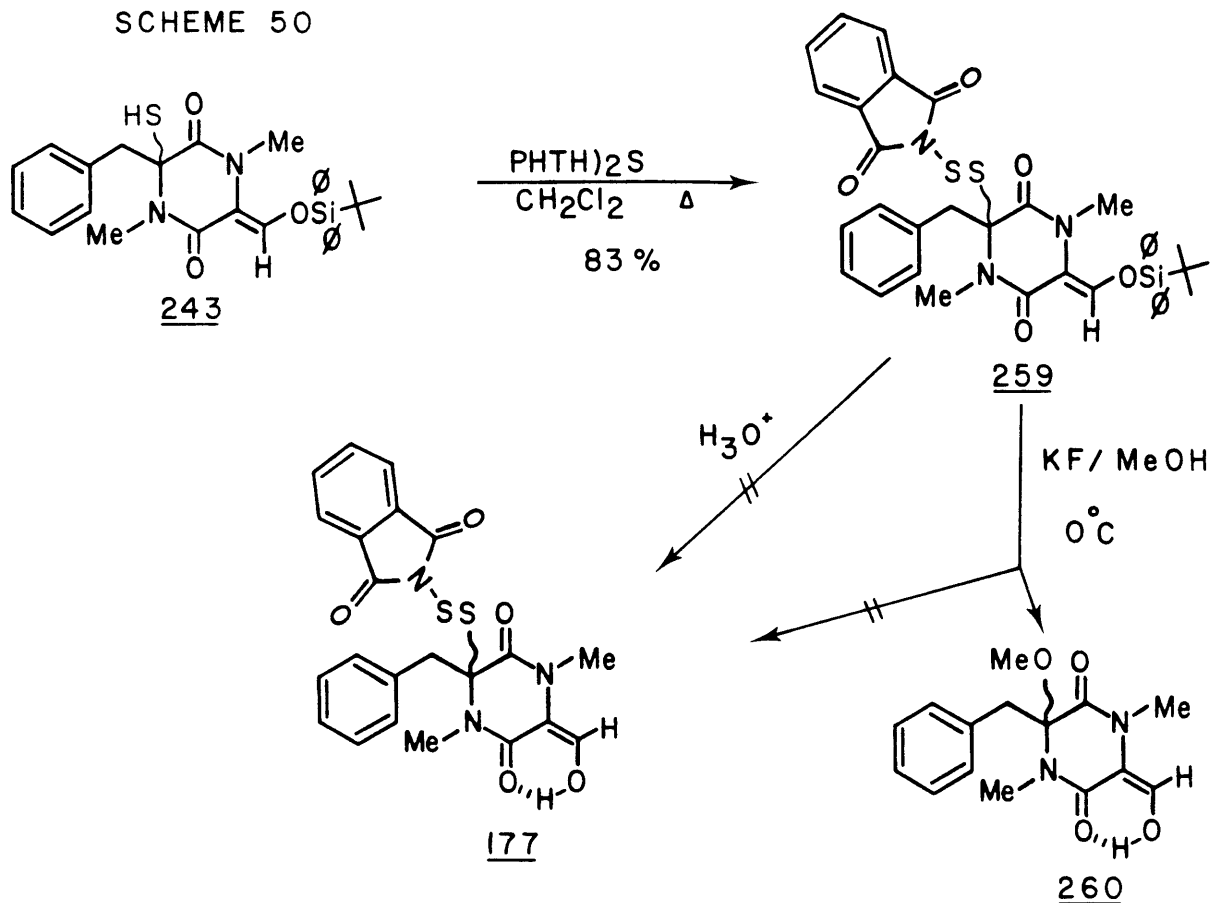




sodium borohydride, followed by an oxidative workup with  $\text{KI}_3/\text{py}$  afforded only trace amounts of hyalodendrin.

As an alternative to this approach, phthalimido disulfide 259 was prepared in the standard manner from thiol 243 (SCHEME 50). Attempts to remove the phthalimido group with  $\text{KF}$  in  $\text{MeOH}$  resulted in several products; the only identifiable product being methoxy enol 260. Attempted hydrolysis of 259 with mild aqueous acid resulted in a complex mixture of products.<sup>132</sup>

SCHEME 50



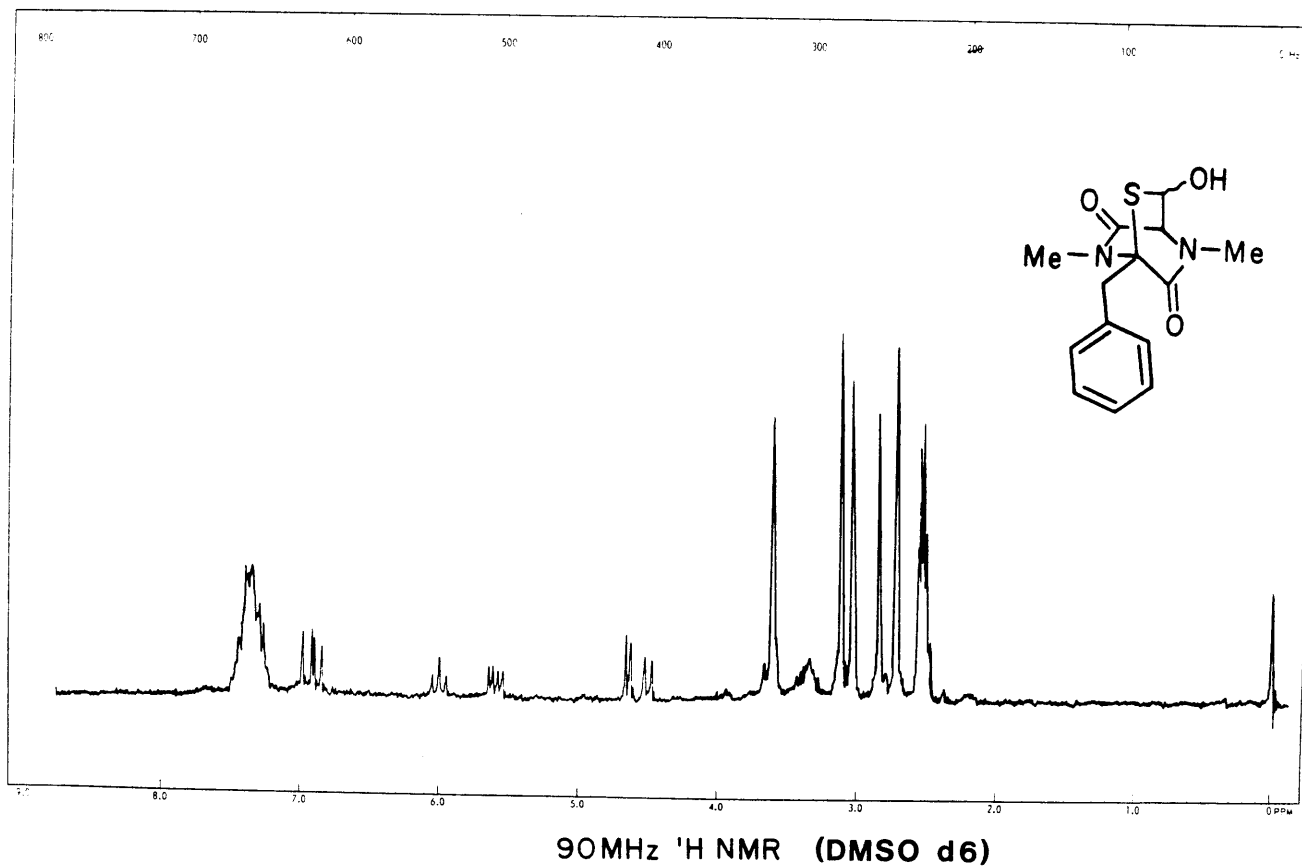
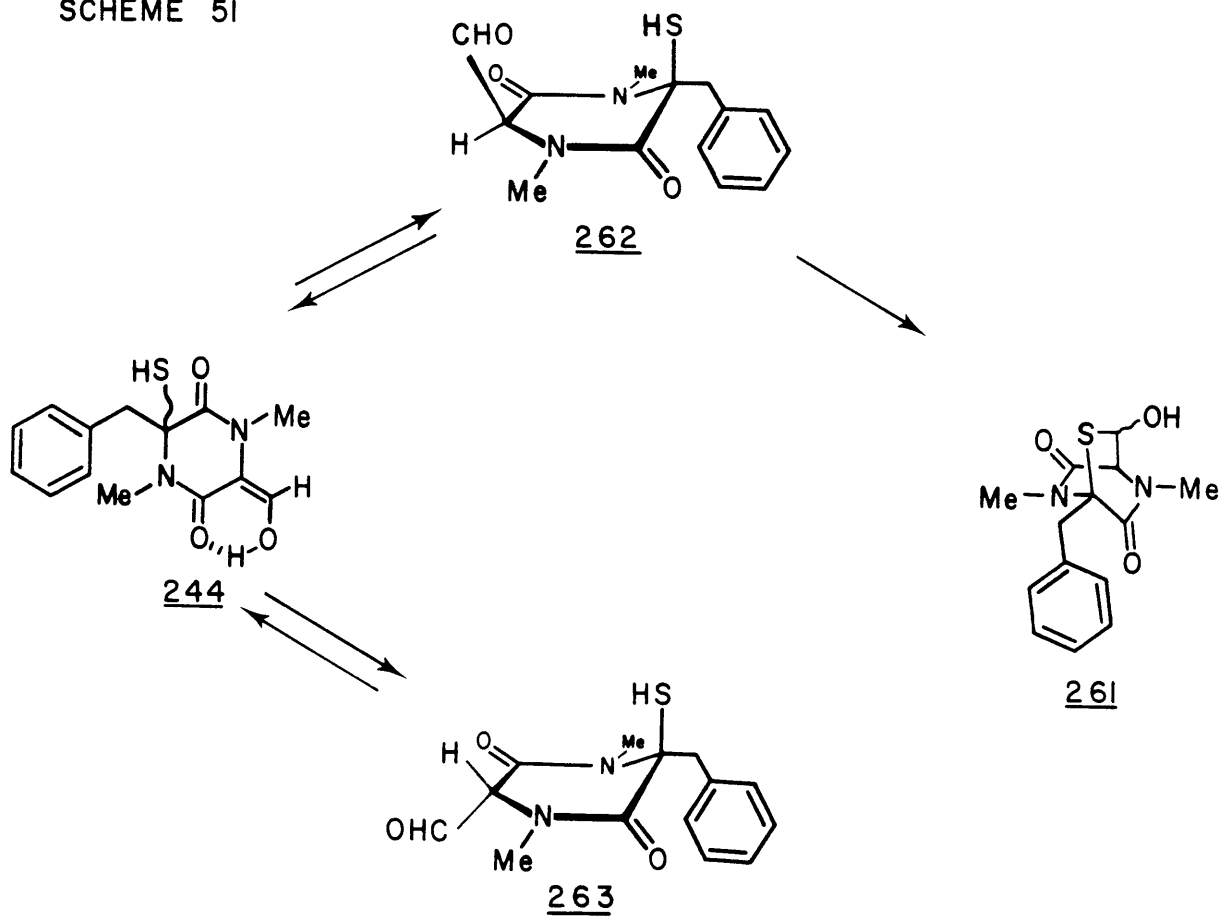
At this point, attention was again directed at elucidating the structure of the compound produced by deprotecting either thiol 243 or methyl disulfide 246

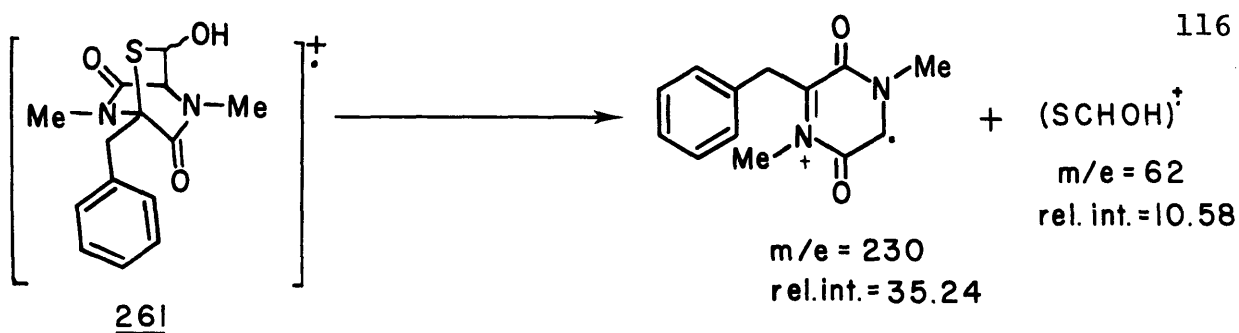
(see SCHEME 44). The IR spectrum of this compound exhibited amide carbonyl absorptions at 1690 and 1650  $\text{cm}^{-1}$ . The enolic stretch, generally around 1600  $\text{cm}^{-1}$  was completely absent. This is consistent with the  $^1\text{H}$  NMR spectrum which lacked the characteristic enolic formyl absorptions (cf.  $^1\text{H}$  NMR spectra in SCHEME 27 and SCHEME 51). The mass spectrum displayed a fairly intense molecular ion ( $M^+=292$ ) for structure 244. A variety of complex structures (dimers, etc.) were considered, but thanks to the suggestion of my colleague Dennis Phillion, structure 261 seemed to fit the data quite nicely.

As shown along with SCHEME 51, the  $^1\text{H}$  NMR spectrum of 261 (d6-DMSO) displays four N-methyl singlets, a broad singlet for the benzylic methylenes, a pair of one proton doublets, a pair of one proton doublets of doublets, a pair of doublets and the aromatic protons. This spectrum is consistent with an approximately 50:50 mixture of diastereomeric hemimercaptals 261.

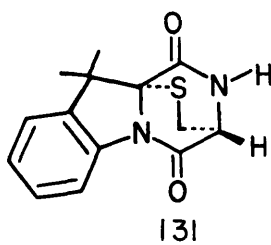
The mass spectrum of 261 provides strong evidence for the assigned structure. As already mentioned, a fairly intense molecular ion ( $m/e=292$ ) is displayed; higher molecular weight peaks are absent. A very intense peak at  $m/e=230$  (see Experimental Section for exact mass measurements) corresponds to loss of the SCHOH bridge; i.e.:

SCHEME 5I





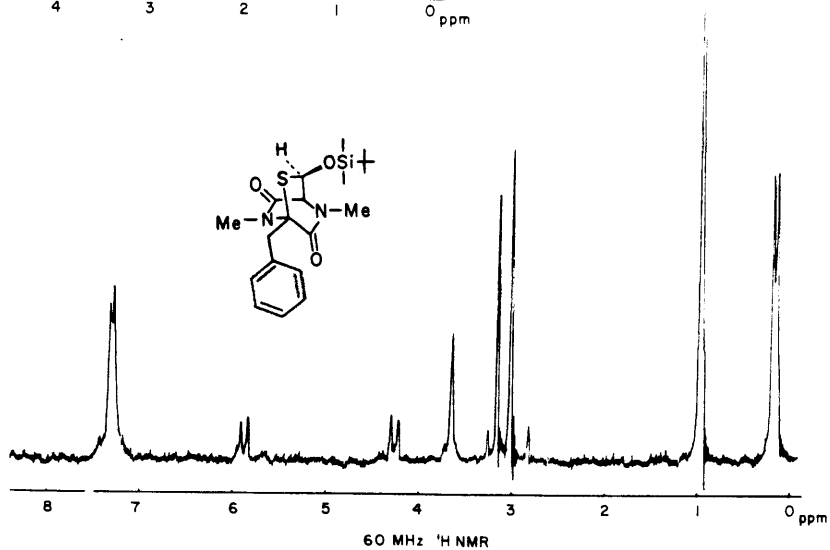
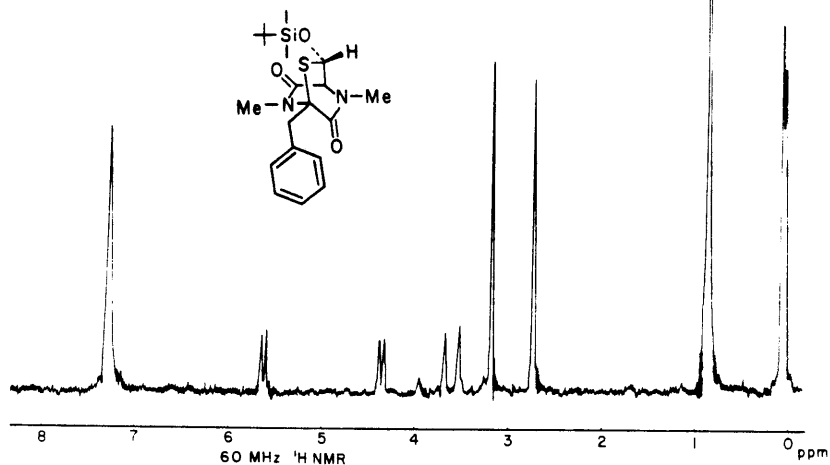
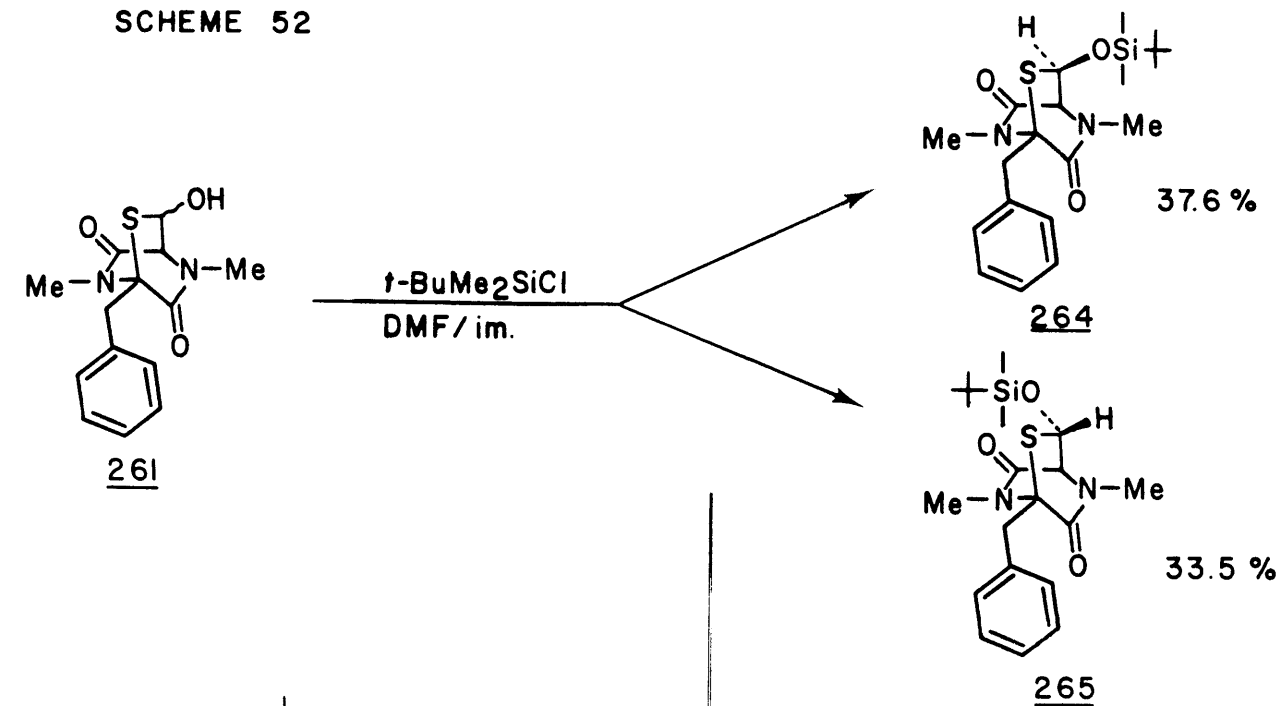
The bridge fragment (SCHOH,  $m/e=62$ ) is also fairly intense. Loss of the epidisulfide ( $\text{S}_2$ )<sup>+</sup> fragment in the mass spectrometer is very characteristic of epidithia-2,5-piperazinediones. A closer analogy, however, is the spectral behavior of the desthiomethylene analog 131 reported by Ottenheijm.<sup>97,98</sup>



Compound 131 also loses the bridge fragment (in this case,  $\text{SCH}_2^+$ ) in the mass spectrometer.

Additional, convincing evidence for the structure of 261 was obtained by silylation of the hemimercaptal alcohol of diastereomers 261 and subsequent chromatographic separation of the O-silyl-hemithioacetals 264 and 265 (SCHEME 52). The <sup>1</sup>H NMR spectra of 264 and 265 are presented along with SCHEME 52 and are fully consistent with the assigned structures. Further-

## SCHEME 52



more, the mass spectral behavior of both 264 and 265 is strikingly similar to that of 261. Although a molecular ion for 264 or 265 was not displayed, both compounds displayed very intense peaks corresponding to  $(\text{M-SCHOSiMe}_2\text{t-Bu})^+$  ( $m/e=230$ ). The fragment  $(\text{S=CHOSiMe}_2\text{t-Bu})^+$  was also observed (see Experimental Section for full listing of low resolution and high resolution mass spectral data). Peaks corresponding to  $(\text{M-C}_4\text{H}_9)^+$ ,  $(\text{M-CH}_3)^+$  and  $(\text{M-C}_7\text{H}_7)^+$  were also measured.

The strained bicyclic structures of 264, 265 and 261 were also evidenced by their IR spectra. The amide carbonyl stretching vibration of (non-bridged) 2,5-piperazinediones is generally  $1660 - 1675 \text{ cm}^{-1}$ ; whereas 264 and 265 exhibited strong carbonyl absorptions at  $1690$  and  $1705 - 1710 \text{ cm}^{-1}$ . Hemimercaptal 261 had an amide stretch at  $1690 \text{ cm}^{-1}$ . The geometry of the bicyclic structure imparts some degree of non-planarity to the amide carbonyl groups and thus accounts for the shift to higher wave numbers. Accordingly, the amide carbonyls of epidithia-2,5-piperazinediones are generally  $1680 - 1690 \text{ cm}^{-1}$  and the amide absorptions for Ottenheijm's<sup>97,98</sup> desthiomethylene analog 131 are  $1705 \text{ cm}^{-1}$ .

Apart from strain and other considerations, the most striking feature of 261 is perhaps the fact that it exists as the hemimercaptal tautomer. Hemimercaptals are generally unstable functionalities<sup>135</sup> and although they can be generated from thiol and carbonyl compounds in the presence of acid

catalysts, attempted isolation of many hemimercaptals generally results in reversion to starting materials.<sup>141</sup> Field and Sweetman<sup>135</sup> have shown that electron withdrawing groups on the carbonyl compound favors the formation of the hemimercaptal. Accordingly, the carboxaldehyde of 262 is expected to be relatively reactive in this sense. In addition, by analogy to the findings of Whitesides<sup>52</sup> on the reducing potentials of  $\omega$ -dithiols, the favorable entropic situation imparted by the relatively planar and rigid diketopiperazine ring on the mutually reactive cis-functionalities favors the bicyclic tautomer 261 over the non-bridged tautomer 244 (see SCHEME 51).<sup>142</sup>

Attempts to sulfenylate 261 under a variety of mildly to strongly basic conditions was investigated, and are summarized below (Table 1). Attempts to isolate 178 were not made. Instead, reaction with the sulfur transfer reagent was followed by reduction with sodium borohydride and oxidation with  $\text{KI}_3 \cdot \text{py}$  as described for the synthesis of hyalodendrin from 247. In the cases summarized, only trace or no detectable quantities of hyalodendrin were observed.

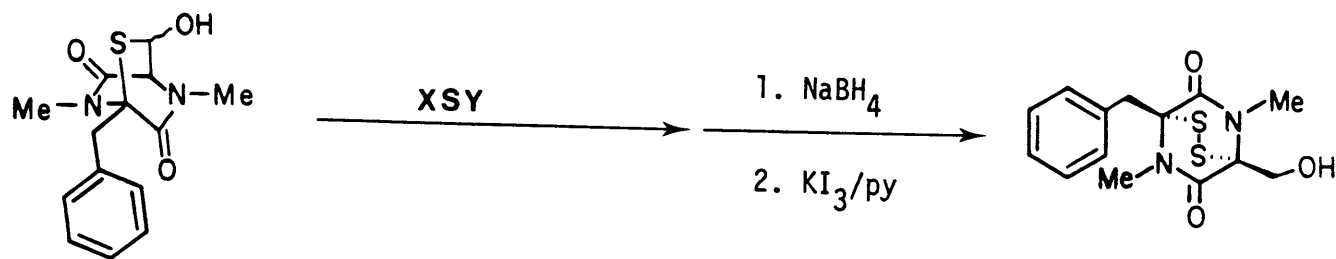


TABLE 1

Attempted sulfenylations of 261

	X-S-Y	solvent	base	catalyst	temperature
1.	<u>188</u>	CH <sub>2</sub> Cl <sub>2</sub>		benzimidazole	25°
2.	SCl <sub>2</sub>	THF	py		0°-25°
3.	<u>191</u>	CH <sub>2</sub> Cl <sub>2</sub>		phthalimide	25°-reflux
4.	<u>191</u>	THF	2eqKO <u>t</u> -Bu		-78°-25°
5.	<u>191</u>	DMSO	2eqKO <u>t</u> -Bu		0°-25°
6.	S <sub>8</sub>	py			reflux
7.	S <sub>8</sub>	DMSO	2eqKO <u>t</u> -Bu		0°-25°
8.	S <sub>2</sub> Cl <sub>2</sub>	DMSO	2eqKO <u>t</u> -Bu		0°-25°
9.	<u>191</u>	THF/MeOH	2eqKO <u>t</u> -Bu		-78° → reflux
10.	SCl <sub>2</sub>	THF	py		-78° → 25°



All of us, whether or not we are warriors have a cubic centimeter of chance that pops out in front of our eyes from time to time. The difference between an average man and a warrior is that the warrior is aware of this, and one of his tasks is to be alert, deliberately waiting, so that when his cubic centimeter pops out he has the necessary speed, the prowess to pick it up.

## Experimental

Melting points (mp) were determined in open-ended capillary tubes on a "Mel-Temp" apparatus, and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer model 567 spectrometer and were obtained as KBr pellets unless otherwise stated. Absorptions are reported in  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR spectra were recorded on the following machines and will be referred to in the experimental section via the assigned letter:

(A) Varian T-60 or Perkin-Elmer R-24B 60 MHz spectrometers without lock

(B) JEOL FX60 Q FT 60 MHz spectrometer with lock

(C) Perkin-Elmer R-20 60 MHz spectrometer with lock

(D) Perkin-Elmer R-22 90 MHz spectrometer with lock

(E) High field pmr were obtained courtesy of the MIT magnet lab 270 MHz.

Chemical shifts are reported in parts per million downfield from  $(\text{CH}_3)_4\text{Si}$  ( $\delta$ ) as internal standard. The following abbreviations are used for spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, sept=septet, m=multiplet. The abbreviation exch.=exchangeable for protons that exchange with a  $\text{D}_2\text{O}$  "shake".

Low resolution mass spectra were obtained on a Varian MAT44 system. High resolution mass spectra were obtained by the MIT-NIH mass spectral facility, Dr. Catherine Costello, director (K. Biemann, principal investigator).

Elemental analyses were performed by Robertson Laboratories, Florham Park, N.J. or Midwest Microlab, Indianapolis, IN.

Analytical thin layer chromatography was performed on either E. Merck 0.2 mm silica gel 60 F0254 layers backed by plastic or Baker-flex 0.25 mm silica gel 1B-F plastic backed plates. Visualization on TLC was achieved with ultraviolet light,  $I_2$  developing chamber and, in the case of thiols and disulfides, 0.1N  $AgNO_3$  spray. Preparative TLC separations were made on 20×20 cm Analtech 2 mm silica gel plates with fluorescent indicator. Column chromatography was carried out using E. Merck silica gel 60 (70–230 mesh). Flash chromatography was performed using E. Merck silica gel 60 (230–400 mesh) according to C. Still. High pressure liquid chromatography was carried out on a Waters Associates Model ALC/GPC 204 system, using a Porasil analytical column and an ultraviolet absorbance detector.

Reagents and solvents were commercial grades and were used as supplied with the following exceptions:

Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Diisopropyl amine was distilled from  $CaH_2$  and kept under  $N_2$  over activated  $4\text{\AA}$  molecular sieves.

Dry ethyl ether was used as obtained in sealed cans. n-butyl lithium was obtained from Ventron and titrated no longer than 1 month prior to use according to W. G. Kofron,<sup>137</sup> and was stored under  $N_2$  in the refrigerator.

When required, dry benzene, toluene, DMF, DMSO, pyridine, HMPA, acetonitrile, and tert-butanol were taken via dry syringe from storage over activated  $4\text{\AA}$  molecular sieves (after distillation from an appropriate dehydrating reagent).

All alkylating or acylating reagents  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ , aldehydes and amines were passed through a short aluminum oxide column prior to use.

Lithium diisopropyl amide (LDA) was freshly prepared by dropwise addition of n-butyllithium in hexane to a stirred solution of diisopropylamine in THF at  $0^\circ$  and was used after stirring 3-5 min.

LDA solutions were transferred via cannula to the reaction vessel using  $\text{N}_2$  pressure. After addition, the flask that contained the LDA was rinsed with ca 1/10 volume of THF that was originally used to prepare the LDA. This solvent rinse was also used when transferring any reaction solution via cannula from one flask to another and will not be referred to in the text of the experiments.

Liquid ammonia for sulfenylations was freshly distilled from freshly prepared  $\text{NaNH}_2$ .

All reactions that are sensitive to oxygen and/or moisture were conducted in glassware that was flame dried under a stream of nitrogen. The nitrogen atmosphere was then replaced with Argon, and the reaction carried out under Argon.

All reactions were magnetically stirred with Teflon coated stir bars unless otherwise noted.

Elemental sulfur for use in sulfenylations in THF was gently warmed with a heat gun under vacuum for 5 min. prior to use (rhombic  $\rightarrow$  monoclinic allotropic conversion).

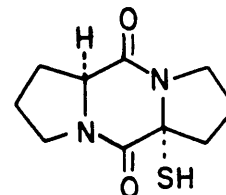
The THF was then added to the sulfur at room temperature to promote dissolution and then cooled in a dry ice-acetone bath.

Reactions run at  $-78^{\circ}\text{C}$  were cooled in either a dry ice-acetone bath or a dry ice-ether bath. Reactions run at  $-100^{\circ}\text{C}$  were cooled in a THF-liquid nitrogen slush bath.

Mass spectral data are recorded by listing the mass number and the relative intensity is given in parantheses.

3-mercapto-propyl-proline anhydride 160

To a stirred solution of propyl-proline anhydride<sup>138</sup> (15.976g, 8.2mmol, 1.0eq) in 20mL THF at -78°C was added a solution of LDA (9.04mmol, 1.1eq) in 5mL THF. The thick, yellow enolate suspension was warmed to 0°C, stirred 30 minutes and added via cannula, to a suspension of elemental sulfur (0.4282g, 13.12mmol, 1.6eq) in 100mL liquid ammonia at -78°C. The mixture was allowed to reflux 1 hour, the ammonia was then evaporated, the residue was quenched with 5% HCl and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The crude mercaptan was dissolved in 50mL absolute ethanol at 0°C and NaBH<sub>4</sub> (1.5g, 39.4mmol, 4.8eq) was added portionwise. After stirring 1 hour at 0°C, the mixture was quenched with 5% HCl and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated to afford 1.6547g (89%) 160 as white crystals mp 128-131°C.



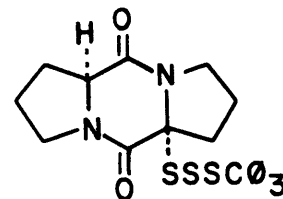
NMR(D) (CDCl<sub>3</sub>): 1.8-2.6 (8H,m); 2.67 (1H,s); 3.55 (4H,m);  
4.35 (1H,t,J=8Hz).

IR: 2495, 1670, 1415, 680.

Mass Spectrum: 226 (M<sup>+</sup>, 0.21); 193 (33) .

3-(trityltrisulfide)-prolyl-proline  
anhydride (163)

To a stirred solution of triphenyl-  
methyl chlorodisulfide<sup>114b</sup> (0.432g, 126mmol,  
1.0eq) in 35mL anhydrous ether at -78°C was  
added a solution of thiol 160 (0.293g, 1.3mmol, 1.03eq) in  
9mL ether. The mixture was stirred for 1 hour at -78°C, 8 hours  
at room temperature, evaporated and the residue separated on a  
silica gel column (eluted with 20% ethanol in ethyl acetate) to  
afford 0.5765g (83%) of trisulfide 163 as white crystals, mp  
158-160°C (recryst, EtOAc).



NMR(D) (CDCl<sub>3</sub>): 1.8-2.7(8H,m): 3.5-3.8(4H,m); 4.4-4.6(1H,m);  
7.45(15H,s).

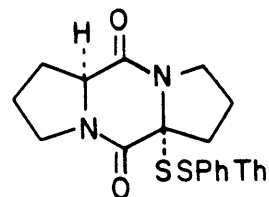
IR: 1670,1490,1480,1440,1400,740,700,680.

Mass Spectrum: 275(0.25); 244(48.7); 192(29.5); 165(100).

Anal. Calcd, for C<sub>29</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S<sub>3</sub>: C, 65.38; H, 5.29; N, 5.25; S, 18.05,

found: C, 66.1; H, 5.58; N, 5.15; S, 18.35.

3-(phthalimido disulfide)-prolylproline  
anhydride 164



To a stirred solution of N-N'-thiobisphthalimide (3.44g, 10.6mmol, 1.2eq) in 120mL methylene chloride at reflux was added a solution of 160 (2.00g, 8.84mmol, 1.0eq) in 30mL CH<sub>2</sub>Cl<sub>2</sub> over a 35 minute period. The mixture was refluxed for 1 hour, cooled and evaporated. The residue was triturated with benzene, filtered and evaporated to afford 3.313g (93%) 164 as white crystals mp 164-166°C (recryst CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O).

NMR(D) (CDCl<sub>3</sub>): 1.8-3.0 (8H,m); 3.35-4.0 (4H,m); 4.87 (1H,t,J=7Hz);  
3.35-4.0 (4H,m); 4.87 (1H,t,J=7Hz); 7.86 (4H,m).

IR: 1780,1740,1705,1670,1645,1275,1045,715

Mass Spectrum (exact mass) m/e= 193.09737(M-SSphth)<sup>+</sup>

C<sub>10</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub> requires 193.09770; 147.03302(phth)<sup>+</sup>

C<sub>8</sub>H<sub>5</sub>NO<sub>2</sub> requires 147.03202.

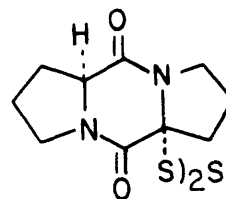
Anal. calcd. for C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub>: C, 53.58; H,4.24; N, 10.4; S, 15.89  
found: C, 53.01; H, 4.33; N, 10.58; S, 15.54.



prolylproline anhydride dimer

trisulfide (166)

To a stirred solution of 164 (0.8877g, 2.2mmol, 1.1eq) in 15mL methylene chloride at reflux was added a solution of thiol 160 (0.4526g, 2.0mmol, 1.0eq) in 10mL methylene chloride. The mixture was refluxed for 5-1/2 hours cooled to room temperature and the solvent removed under reduced pressure. The residue was separated on a silica gel column (eluted with 20% ethanol in ethyl acetate) to afford 0.9303g (96.4%) trisulfide 166 as white crystals mp 153-145°C (recryst EtOAc/hexane).



NMR (D) ( $\text{CDCl}_3$ ): 1.7-2.9 (16H, m); 3.3-4.0 (8H, m); 4.3-4.7 (2H, m).

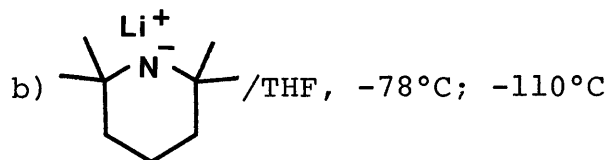
IR: 1670, 1440, 1395, 1160, 660.

Mass Spectrum: 256(1.31); 224(0.53); 193(19.96); 96(19.58); 41(100).

Summary of attempted cyclizations of 163 and 164.

---

164: a)  $\phi_3C^-Li^+$  /THF,  $-78^\circ C$



c) KH/18-Crown-6/THF,  $-78^\circ C$

d) LDA · HMPA/THF,  $-100^\circ C$

e) n-BuLi/THF,  $-100^\circ C$

f)  $KOt\text{-}Bu$ /THF,  $-78^\circ C$

g)  $BF_3 \cdot Et_2O$ /THF/ $CH_2Cl_2$ /catalytic 2,6-lutidine

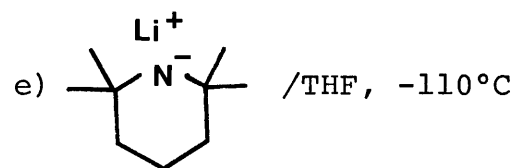
h)  $BF_3 \cdot Et_2O$ / $CH_2Cl_2$ /"proton sponge"

163: a) NaNH<sub>2</sub>/THF,  $-110^\circ C$

b)  $(Me_3Si)_2N^-Li^+$ /THF/ $Et_2O$ ,  $110^\circ C$

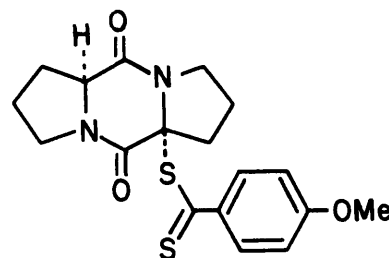
c) LDA/THF,  $-78^\circ C$ ;  $-100^\circ C$

d) KH/THF,  $25^\circ C$



3-(p-methoxyphenyl)thionothio-propyl-proline anhydride (170)

To a stirred solution of thiol 160 (0.104g, 0.46mmol, 1.0eq) in 3.5mL THF at 0°C was added a solution of p-methoxyphenyl thiono acid chloride<sup>116</sup> 171 in 1mL



THF. After stirring 90 minutes at 0°C and 1 hour at room temperature, the mixture was filtered, evaporated and separated on preparative silica gel TLC (eluted with EtOAc) to afford 0.0523g (30%) 170 as an unstable pale violet oil.

NMR(D) (CDCl<sub>3</sub>): 1.9-2.9 (8H,m); 3.5-3.8 (4H,m); 3.90 (3H,s)  
4.7-5.0 (1H,m); 6.98 (2H,d,J=9Hz); 7.90 (2H,d,  
J=9Hz).

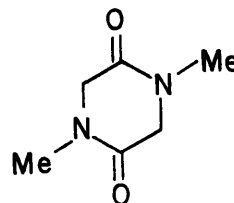
IR(NaCl,neat): 1660,1595,1505,1415,1310,1260,1210,1165,1025,900,  
840,700.

Mass Spectrum: 192(82.4); 152(3.9); 135(100); 107(11.6), 77(23.1).

\*In addition, 0.0336g (38%) of dehydro compound (173)<sup>68</sup> was isolated from this reaction.

1,4-dimethyl-2,5-piperazinedione (86)  
(sarcosine anhydride)

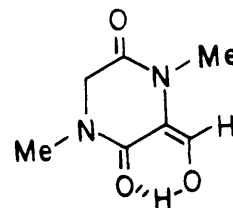
Sarcosine anhydride was prepared most efficiently by a modification of the procedure of Chemizard and David.<sup>139</sup>



Sarcosine was dissolved in  $\text{H}_2\text{O}$  with a 10% volume of 10%  $\text{H}_2\text{SO}_4$  in MeOH. The mixture was refluxed for 18 hours and then boiled to dryness. The resulting black residue was triturated with  $\text{CH}_2\text{Cl}_2$  and stirred with 15% weight activated carbon for 3 hours. Filtration through silica gel and recrystallization from ethanol several times afforded 25-50% yields of sarcosine anhydride as white needles mp  $148^\circ\text{C}$ .

1,4-dimethyl-3-formyl-2,5-piperazine-  
dione (183)

Freshly dried, powdered, 1,4-dimethyl-2,5-piperazinedione (16.0g, 112.5mmol, 1.0eq) and powdered sodium methoxide (13.0g, 24.14mmol, 2.14eq) were placed in the reaction vessel under a nitrogen atmosphere. 150mL of dry THF was added at 0°C. After stirring the mixture for 5 minutes at 0°C, freshly distilled ethyl formate (45.5mL, 562.7mmol, 5.0eq) was added dropwise. After the addition was complete, the thick, white suspension was allowed to come to room temperature. 50mL of THF was added and the mixture was vigorously stirred 1 hour at room temperature, 1 hour at reflux and an additional 3 hours at room temperature. The resulting thick, white suspension was cooled to 0°C, filtered and washed thoroughly with dry THF. After drying the white cake in vacuo for 12 hours, the product was dissolved in 500mL H<sub>2</sub>O (the resulting pH=10) and 1 N HCl was added until the pH=3-3.5. The water was evaporated under reduced pressure and the resulting white solid was dried in vacuo, ground to a fine powder and washed in a 150mL medium frit with CHCl<sub>3</sub>. The filtrate was evaporated under reduced pressure, affording 18.3g (95.5%) (183) white crystals mp 143-145°C (recryst. CHCl<sub>3</sub>).



NMR(D) (CDCl<sub>3</sub>): 2.99(3H,s); 3.09(3H,s); 4.02(2H,s); 7.00(1H,d,  
J=11Hz.); 12.47(1H,d,J=11Hz., D<sub>2</sub>O exch.).

IR: 3400, 1660, 1615, 1525, 1480, 1435, 1422, 1407, 1360,  
1270, 1210, 1150, 930, 870, 470

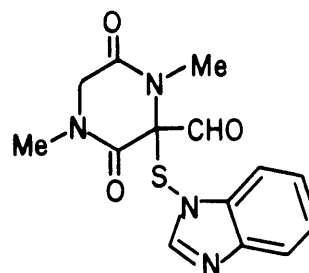
Anal. Calcd. for  $C_7H_{10}N_2O_3$ : C, 49.41; H, 5.92; N, 16.46

found: C, 49.30; H, 5.97; N, 16.30

Mass Spectrum: calcd. for  $C_7H_{10}N_2O_3$ : 170.06914

found: 170.0690

1,4-dimethyl-3-(1-thiobenzimidazolyl)-  
3-carboxaldehyde-2,5-piperazinedione (185)

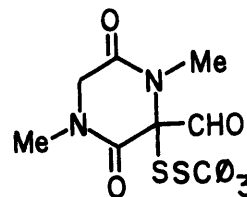


To a stirred solution of formyl  
piperazinedione 183 (0.1333g, 0.78mmol,  
1.0eq) in 5mL CH<sub>2</sub>Cl<sub>2</sub> was added a solution  
of 1,1'-thiobis-benzimidazol (188) (0.2084g, 0.78mmol, 1.0eq)  
in 5mL CH<sub>2</sub>Cl<sub>2</sub> over a 5 minute period. The mixture was allowed  
to stir for 1 hour at room temperature, filtered and the  
solvent removed under pressure to afford 0.2387g (96%) aldehyde  
185 as an unstable white foam (1/2 life ca. 1 hour).

NMR(A) (CDCl<sub>3</sub>): 2.85(3H,s); 2.96(3H,s); 3.98(2H,s);  
7.0-7.8(4H,m); 8.3(1H,s); 9.2(1H,s).

1,4-dimethyl-3-(trityldithio)-3-carboxaldehyde-2,5-piperazinedione (192)

To a stirred solution of 183 (1.407g, 8.26mmol, 1.0eq) in 30mL THF at -78°C was added triethylamine (1.15mL, 8.26mmol, 1.0eq). To this mixture was added a solution of triphenylmethyl chlorodisulfide (2.8345g, 8.26mmol, 1.0eq) in 15mL THF over a 15 minute period. After addition, the resulting white suspension was stirred 1 hour at -78°C, warmed to 0°C, and filtered to remove Et<sub>3</sub>N·HCl. Evaporation of the solvent afforded 3.916g (99.6%) of disulfide aldehyde 192 as a brittle, white foam.



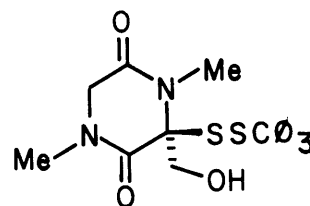
NMR(A) (CDCl<sub>3</sub>): 2.67(3H,s); 2.75(3H,s); 4.75(2H,s); 7.23(15H,s); 8.65(1H,s).

IR: 1735,1670,1490,1440,1390,735,700.

Mass Spectrum: m/e = 169.06437 (M-SStr)<sup>+</sup> C<sub>7</sub>H<sub>9</sub>N<sub>2</sub>O<sub>3</sub> requires 169.06534



1,4-dimethyl-3-(trityldithio)-  
3-hydroxymethyl-  
2,5-piperazinedione (193)



To a stirred solution of disulfide aldehyde 192 (1.19g , 2.5mmol, 1.0eq) in 10mL THF at -78°F was added a solution of lithium tri-*t*-butoxyaluminum hydride (0.7628g, 3.0mmol, 1.2eq) in 7mL THF. The mixture was allowed to stir 15 min. at -78°C and 1 hour at room temperature. The mixture was quenched with 2N HCl in MeOH, poured into water and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on a silica gel column (eluted with EtOAc) to afford 0.7756g (65%) of alcohol disulfide 193 as white crystals mp 179-180°C (recryst. EtOAc/CH<sub>2</sub>Cl<sub>2</sub>).

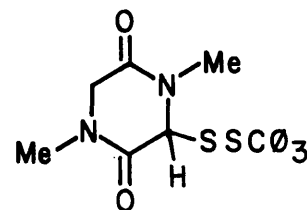
NMR(D) (CDCl<sub>3</sub>): 3.02(6H,s); 3.21(1H,exch. t, J=7Hz); 3.79 (1H,q,J<sub>AX</sub>=7Hz, J<sub>AB</sub>=12Hz); 3.99(1H,1/2ABq,J=17Hz); 4.27 (1H,q,J<sub>AX</sub>=7Hz, J<sub>AB</sub>=12Hz); 4.31(1H,1/2ABq,J=17Hz); 7.34(15H,s).

IR: 3390 (broad), 1670, 1660, 1490, 1440, 1390, 740, 700.

Mass Spectrum: 243(91.9); 171(17.8); 165(100).

1,4-dimethyl-3-(trityldithio)-2,5-piperazinedione (194) from deformatylation of (192)

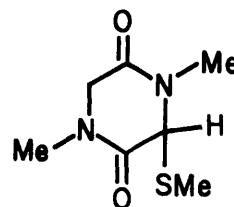
Attempted chromatography on silica gel; attempted reduction with  $\text{NaBH}_4$  followed by acidic workup and chromatography; and attempted reduction with catecholborane followed by workup and chromatography of disulfide carboxaldehyde 192 all resulted in the formation of deformatylated disulfide 194 as a brittle foam, in varying amounts.



NMR (D) ( $\text{CDCl}_3$ ): 2.52 (3H, s); 2.88 (3H, s); 3.94 (1H, 1/2ABq,  $J=16\text{Hz}$ );  
 3.80 (1H, s); 4.39 (1H, 1/2ABq,  $J=16\text{Hz}$ );  
 7.2-7.6 (15H, m).

IR: 1680, 1480, 1440, 1295, 750, 735, 700

1,4-dimethyl-3-methylthio-  
2,5-piperazinedione (199)



Methylthio carboxaldehyde 212  
(1.3866g, 6.42mmol) was slurried into  
silicagel (70-230 mesh; ca. 50g) with  
ethyl acetate. The thick slurry was stirred vigorously at  
room temperature for 36 hours, filtered and washed thoroughly  
with ethyl acetate. Evaporation of the solvent under reduced  
pressure afforded 1.1184g (92.6%) of 199 as white crystals.  
mp 105-106.5°C (recryst. EtOAc/Et<sub>2</sub>O)

NMR(A) (CDCl<sub>3</sub>): 2.20(3H,s); 2.98(3H,s); 3.02(3H,s); 3.84(1H,  
1/2ABq,J=17Hz); 4.13(1H,1/2ABq,J=17Hz); 4.70(1H,s).

IR: 1675, 1485,1410,1335,1305,1020,760.

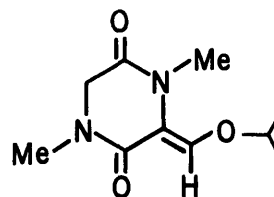
Mass Spectrum: 187(M<sup>+</sup>,1.86); 173(1.05); 141(56.83); 113(46.29);  
42(100).

<sup>13</sup>C NMR(B) (CDCl<sub>3</sub>,15.015MHz)

δTMS: 13.096(SMe); 31.605(NMe); 33.164(NMe); 50.893(methylene);  
64.466(methinyl); 162.658(amide CO); 163.892(amide CO).

1,4-dimethyl-3-(isopropoxy)formyl-  
2,5-piperazinedione (200)

To a stirred solution of 183  
(0.1382g, 0.81mmol, 1.0eq) in 5 mL H<sub>2</sub>O  
at 0°C was added (0.81mL, 0.81mmol,



1eq) 1 N KOH. After addition, the mixture was allowed to  
come to room temperature and the H<sub>2</sub>O removed in vacuo. The  
resulting yellow, oily residue was dissolved in 2mL THF and  
2mL DMF at room temperature. To this solution was added  
isopropyl iodide (0.16mL, 1.62mmol, 2.0eq). The mixture was  
stirred 12 hours at room temperature, the solvent evaporated,  
and the residue triturated with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> soluble  
residue was separated on preparative silica gel TLC(eluted  
with EtOAc) to afford 0.1359g (79%) 200 as white needles  
mp 100-102°C.

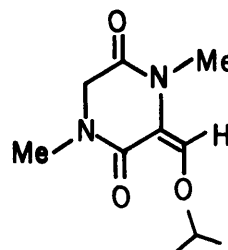
NMR(D) (CDCl<sub>3</sub>): 1.35 (6H,d,J=6Hz); 2.97(3H,s); 3.28(3H,s);  
3.95 (2H,s); 4.19(1H,sept.); 7.0(1H,s).

IR: 1675, 1615, 1385, 1210, 1100

MS: 212 (18, M<sup>+</sup>); 170 (100); 141 (69)

1,4-dimethyl-3(E)-(isopropoxy)formyl-  
2,5-piperazinedione (201)

Sodium salt 182, (prepared as for 183; 6.0mmol, 1.0eq) was suspended in 10mL THF at 0°C and isopropyl iodide (0.7mL, 7.2mmol, 1.2eq) was added. The mixture was heated to reflux and vigorously stirred for 1 hour. An additional 6 eq of isopropyl iodide was added and refluxing continued for 36 hours. The mixture was cooled to room temperature stirred 12 hours and the solvent removed under reduced pressure. The residue was taken up in ethanol and separated on preparative silica gel TLC (eluted with 20% EtOH in EtOAc) to afford 0.1521g (40%) Z-isomer 200\* and 0.062g (15.5%) of E-isomer 201. For 201:



NMR(A) ( $\text{CDCl}_3$ ): 1.40(6H,d,J=6Hz); 2.97(3H,s); 3.11(3H,s);  
3.96(2H,s); 4.13(1H,sept,J=6Hz); 6.52(1H,s)

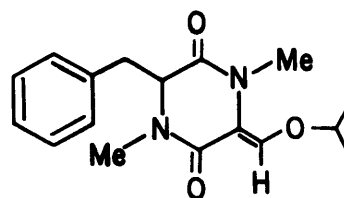
IR: 1675, 1620, 1220, 1100

Mass Spectrum: 212( $\text{M}^+$ ,12.38); 170(100); 141(68.25)

\*For 200 (Z-isomer), see separate experimental.

1,4-dimethyl-3-(isopropoxy)formyl-  
6-benzyl-2,5-piperazinedione (204)

To a stirred solution of 200  
(0.9611g, 4.53mmol, 1.0eq) in 30mL  
THF at -78°C was added a solution of  
LDA (5.2mmol, 1.15eq) in 5mL THF.



After stirring the bright yellow enolate suspension for 3 minutes at -78°C, the mixture was transferred via cannula into a solution of benzyl bromide (2.7mL, 22.6mmol, 5.0eq) in 30mL THF at -78°C. The mixture was stirred 20 minutes at -78°C, warmed to room temperature, poured into a saturated sodium chloride solution and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on a silica gel column (eluted with 25%EtOH in EtOAc) to afford 1.2046g (88%) 204 as a clear oil which crystallized on standing in ether mp 142-144°C.

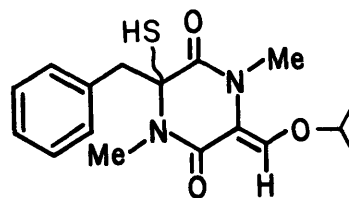
NMR(D) (CDCl<sub>3</sub>): 1.23(3H,d,J=6Hz); 1.25(3H,d,J=6Hz); 2.87(3H,s);  
3.09(2H,d,J=5Hz); 3.17(3H,s); 3.95(1H,sept, J=6Hz);  
4.17(1H,t,J=5Hz); 6.50(1H,s); 7.0-7.3(5H,m).

IR: 1745,1680,1600,750,710.

Mass Spectrum: 302(M<sup>+</sup>,3.3); 91(50.4); 42(100)

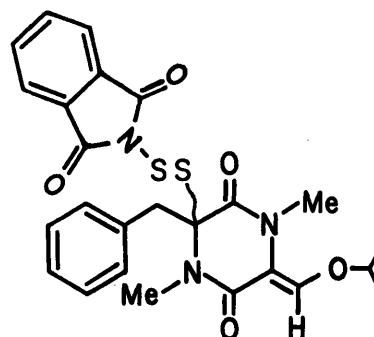
1,4-dimethyl-3-(isopropoxy)formyl-6-mercapto-6-benzyl-2,5-piperazinedione (205)

To a stirred solution of 204 (0.5564g, 1.84mmol, 1.0eq) in 8mL THF at -78°C was added a solution of LDA (2.30mmol, 1.25eq) in 2mL THF. The resulting greenish-yellow enolate suspension was stirred 3 minutes at -78°C and added, via cannula, to a suspension of elemental sulfur (0.0961g, 2.94mmol, 1.6eq) in 20 mL liquid ammonia at -78°C. The mixture was warmed to -33°C and allowed to reflux for 90 minutes. The ammonia was allowed to evaporate, and stirring continued for 1 hour at room temperature. The mixture was quenched with 5% HCl and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The resulting residue was dissolved in 25mL EtOH at 0°C and NaBH<sub>4</sub> (0.3338g, 8.83mmol, 4.8eq) was added portionwise. The mixture was stirred 1 hour at 0°C and an additional 4.8eq of NaBH<sub>4</sub> was added. After stirring at 0°C for 1 hour, the mixture was quenched with 5% HCl, poured into water and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated to afford 0.6449g (quant.) 205 as a yellow oil.



NMR(D) (CDCl<sub>3</sub>): 1.27(3H,d,J=6Hz); 1.29(3H,d,J=6Hz); 3.10(3H,s); 3.25(1H,s); 3.30(3H,s); 3.35(1H,1/2ABq,J=14Hz); 3.81(1H,1/2ABq,J=14Hz); 4.04(1H,sept,J=6Hz); 6.80(1H,s); 6.9-7.35(5H,m).

1,4-dimethyl-3-(isopropoxy)formyl-6-benzyl-6-(phthalimidodisulfide)-2,5-piperazinedione (206)



To a stirred solution of N-N'-thiobisphthalimide (0.1185g, 0.365mmol, 1.0eq) in 5mL of refluxing  $\text{CH}_2\text{Cl}_2$  was added a solution of thiol 205 (0.1222g, 0.365mmol, 1.0eq) in 2mL  $\text{CH}_2\text{Cl}_2$ . The mixture was refluxed for 15 minutes, evaporated and the residue triturated with benzene. The benzene soluble residue was separated on preparative silica gel TLC (eluted with 10% EtOAc in  $\text{CH}_2\text{Cl}_2$ ) to afford 0.0548g (30%) of phthalimido disulfide 206 as white crystals mp  $180^\circ$  (decomp) (recryst  $\text{Et}_2\text{O}$ /hexane)

NMR(D) ( $\text{CDCl}_3$ ): 1.23(3H,d,J=6Hz); 1.31(3H,d,J=6Hz);  
3.10(3H,s); 3.14(1H,1/2ABq,J=13Hz);  
3.18(3H,s); 3.62(1H,1/2ABq,J=13Hz);  
4.03(1H,sept,J=6Hz); 6.76(1H,s); 6.9-7.3  
(5H,m); 7.7-8.0(4H,m).

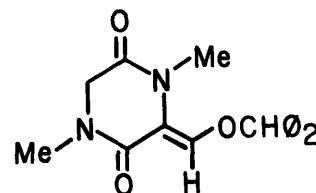
IR: 1785, 1770, 1740, 1680, 1360, 1370, 1100, 715.

Mass Spectrum: 365(0.1); 333(0.13); 300(2.91); 258(24.4);  
178(2.52); 147(61.77); 91(100)



1,4-dimethyl-3-(benzhydryloxy)formyl-  
2,5-piperazinedione (207)

To a stirred solution of 183  
(3.583g, 21.0mmol, 1.0eq) in 25mL  
methanol was added (23.1mL, 23.1mmol,  
1.1eq) of 1N KOH at room temperature.



The solvents were evaporated and the resulting yellow powder was dried in vacuo. This solid, potassium salt was suspended in 50mL dry DMF with a few mg KI. To this suspension was added benzhydryl chloride (11.2mL, 63mmol, 3.0eq) dropwise at room temperature. The mixture was stirred for 12 hours at room temperature and heated for 20 minutes on a steam bath. An additional 3.73mL (1.0eq) of benzhydryl chloride was added and stirring continued for 10 minutes on the steam bath and 30 minutes at room temperature. The DMF was removed under reduced pressure and the resulting oily residue was poured into a saturated sodium chloride solution. The aqueous phase was extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>, the combined extracts dried over anhydrous sodium sulfate, filtered, evaporated and separated on a silica gel column (eluted with EtOAc) to afford 3.2497g (46%) 207 as a brittle, white foam.

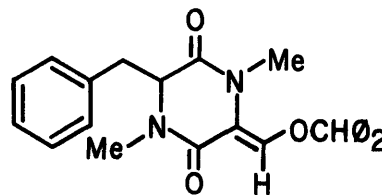
NMR(D) (CDCl<sub>3</sub>): 2.90(3H,s); 3.43(3H,s); 3.94(2H,s); 5.96(1H,s);  
7.12(1H,s); 7.35(10H,s).

IR(NaCl,CHCl<sub>3</sub>): 1680,1485,1410,1335,1305,1020,760.

Mass Spectrum: 336(M<sup>+</sup>, 0.22); 166(100).

1,4-dimethyl-3-(benzhydryloxy)formyl-6-benzyl-2,5-piperazinedione (208)

To a stirred solution of 207 (2.694g, 8.0mmol, 1.0eq) in 55mL THF at 78°C was added a solution of LDA(10.0mmol, 1.25eq) in 5mL THF. After stirring the thick greenish suspension for 3 minutes at -78°C, this mixture was transferred via cannula, into a solution of benzyl bromide (4.75mL, 40mmol, 5.0eq) in 20mL THF at -78°C. The dark, orange colored solution was allowed to stir 15 minutes at -78°C, 1 hour at room temperature, poured into a solution of 5% HCl saturated with sodium chloride and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on a silica gel column (eluted with EtOAc) to afford 1.1292g (33%) (208) as an oil.



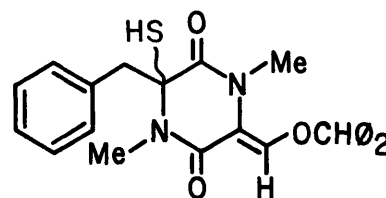
NMR(D) (CDCl<sub>3</sub>): 2.82(3H,s); 3.05(2H,d,J=5Hz); 3.28(3H,s);  
4.15(1H,t,J=5Hz); 5.70(1H,s); 6.60(1H,s);  
7.10(5H,s); 7.32(10H,m).

IR(NaCl,neat); 1725, 1680, 1600, 1490, 1450, 1390, 1180, 1160,  
750, 700.

Mass Spectrum: 259(0.64); 167(100); 91(95)

1,4-dimethyl-3-(benzhydryloxy)formyl-6-mercapto-6-benzyl-2,5-piperazinedione (209)

To a stirred solution of 208 (1.0876g, 2.55mmol, 1.0eq) in 18mL THF at -78°C was added a solution of LDA (3.18mmol, 1.25eq) in 2mL THF. The resulting green colored enolate suspension was stirred 5 minutes at -78°C and added via cannula to a suspension of elemental sulfur (0.1332g, 4.08mmol, 1.6eq) in 30mL liquid ammonia at -78°C. The mixture was warmed to -33°C and allowed to reflux for 90 min. The ammonia was allowed to evaporate, the mixture quenched with 5% HCl and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The resulting residue was dissolved in 25mL EtOH plus 10mL THF at 0°C and NaBH<sub>4</sub> (0.4627g, 12.24mmol, 4.8eq) was added portion-wise. After stirring at 0°C for 1 hour, the mixture was quenched with 5% HCl, poured into water and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated to afford 1.1777g (>90%) 209 as a brittle foam.

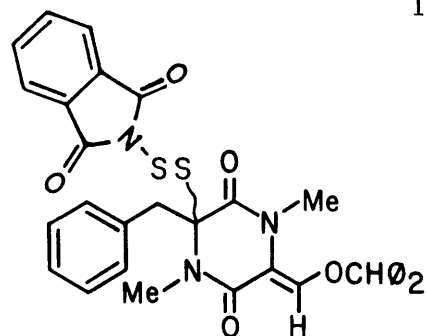


NMR(D) (CDCl<sub>3</sub>): 3.10(3H,s); 3.23(1H,s); 3.22(1H,1/2ABq, J=14Hz);  
3.42(3H,s); 3.80(1H,1/2ABq, J=14Hz); 5.80(1H,s);  
6.99(1H,s); 6.9-7.4(15H,m).

IR: 1675, 1620, 1495, 1450, 1390, 1360, 1175, 750, 700

Mass Spectrum: 258(.9); 167(77); 105(100); 91(96).

1,4-dimethyl-3-(benzhydryloxy)formyl-  
6-benzyl-6-(phthalimidodisulfide)-  
2,5-piperazinedione (210)



To a stirred solution of N-N'-thiobisphthalimide (0.2364g, 0.73mmol, 1.2eq) in 8.5mL of refluxing CH<sub>2</sub>Cl<sub>2</sub> was added a solution of thiol 209 (0.2785g, 0.6mmol, 1.0eq) in 1.5mL CH<sub>2</sub>Cl<sub>2</sub>. The mixture was refluxed for 1 hour and then allowed to stir at room temperature overnight. The solvent was evaporated and the residue triturated with THF. The THF soluble residue was separated on preparative silica gel TLC (eluted with 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to afford 0.2178g (57%) of phthalimido-disulfide 210 as a brittle, white foam.

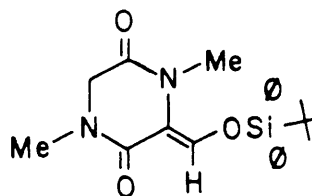
NMR(D) (CDCl<sub>3</sub>): 3.09(3H,s); 3.15(1H,1/2ABq,J=15Hz);  
3.32(3H,s); 3.62(1H,1/2ABq,J=15Hz);  
5.83(1H,s); 6.92(1H,s); 6.95-7.5(15H,m);  
7.6-8.0(4H,m).

IR: 1785,1740,1710,1680,1665,1620,1495,1360,1270,1180,1165,  
715,700.

Mass Spectrum: 425(0.49); 258(6.48); 167(100).

1,4-dimethyl-3-(t-butyldiphenylsiloxy)  
formyl-2,5-piperazinedione (211)

To a stirred suspension of 183  
(17.02g, 100mmol, 1.0eq) in 50mL THF  
and 200mL absolute ethanol at 0°C was  
added, dropwise, a 50mL THF solution of  
potassium tert-butoxide over a 20 min. period. After stirring  
the clear, yellow solution 15 min. at 0°C, the solvents were  
evaporated and the solid, yellow residue dried in vacuo for  
12 hours. This yellow, powdery solid was suspended in 90mL  
of dry DMF, and tert-butyldiphenylsilyl chloride<sup>140</sup> (30.0mL,  
115mmol, 1.15eq) was added dropwise at room temperature. A  
mild, exothermic reaction ensues, leaving a clear yellow-orange  
solution. Stirring was continued an additional 48 hours at room  
temperature. The solvent was evaporated in vacuo and the residue  
partitioned between 0.1N HCl and CH<sub>2</sub>Cl<sub>2</sub>. The aqueous layer was  
thoroughly extracted with CH<sub>2</sub>Cl<sub>2</sub>, the combined extracts were  
dried over anhydrous sodium sulfate, filtered, evaporated and  
trituated with pentane affording 34.7g (85%) 211 as white  
crystals, mp 127-129°C (recryst. CH<sub>2</sub>Cl<sub>2</sub>). An additional 0.76g of  
211 was obtained from the mother liquors by distilling off  
residual silyl compounds (total yield 87%).

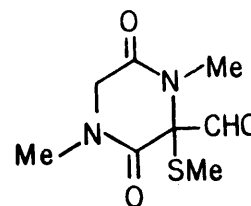


NMR(D) (CDCl<sub>3</sub>): 1.15(9H,s); 2.93(3H,s); 3.53(3H,s); 3.97(2H,s);  
7.09(1H,s); 7.3-7.8 (10H,m).

IR: 1680, 1630, 1590, 1200, 1165, 800, 712, 700

Mass Spectrum: calcd. for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>Si: 408.18692  
found: 408.18496

1,4-dimethyl-3-methylthio-3-carbox-  
aldehyde-2,5-piperazinedione (212)



To a stirred solution of 183 (3.1762g, 8.66mmol, 1.0eq) in 100 mL THF at  $-100^{\circ}\text{C}$  was added  $\text{Et}_3\text{N}$  (2.74mL, 19.6mmol, 1.05eq). To this solution was added freshly prepared  $\text{CH}_3\text{SCl}$ <sup>124,125</sup> (2.0027g, 24.26mmol, 1.3eq) in 20 mL THF over a 10 minute period. After the addition was complete, the resulting white suspension was stirred at  $-100^{\circ}\text{C}$  for 30 minutes, allowed to warm to  $0^{\circ}$  and filtered, cold, to remove  $\text{Et}_3\text{N}\cdot\text{HCl}$ . Evaporation of the solvent under reduced pressure afforded (4.2333g, 100%) pure 212 mp  $98-100^{\circ}\text{C}$  (recryst.  $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ )

NMR(A) ( $\text{CDCl}_3$ ); 2.17(3H,s); 2.92(3H,s); 3.04(3H,s);  
4.03(1H,1/2ABq,J=17Hz); 4.21(1H,1/2ABq,  
J=17Hz); 9.43(1H,s).

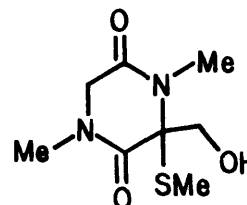
IR: 1740, 1660, 1395, 1008, 735

Anal.calcd. for  $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_3\text{S}$ : C, 44.43; H,5.59; N,12.95; S,14.82  
found: C, 44.41; H,5.76; N,12.82, S,15.02

Mass spectrum;  $m/e=169.06117$  ( $\text{M}-\text{SCH}_3$ )<sup>+</sup>  $\text{C}_7\text{H}_9\text{N}_2\text{O}_3$  requires 169.06131;  
( $\text{M}-\text{CHO}$ )<sup>+</sup>  $\text{C}_7\text{H}_{11}\text{N}_2\text{O}_2\text{S}$  requires 187.05412.

1,4-dimethyl-3-hydroxymethyl-3-methylthio-  
2,5-piperazinedione (213)

To a stirred solution of 212 (1.6969g, 7.85mmol, 1.0eq) in 20mL THF at -78°C was added a suspension of  $\text{LiAl}(\text{tert-BuO})_3\text{H}$  (2.992g, 11.77mmol, 1.5eq) in 30 mL THF.



The mixture was stirred at -78°C for 1 hour, allowed to come to room temperature and stirred an additional 3 hours. The reaction was quenched with 1N HCl, poured into a saturated sodium chloride solution and extracted thoroughly with  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The residue was taken up in a small volume of  $\text{CH}_2\text{Cl}_2$  and passed through a plug of silica gel, affording, after removal of the solvent 1.5709g (92%) pure alcohol 213 mp 104-106°C (recryst.  $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}/\text{EtOAc}$ ).

NMR(D) ( $\text{CDCl}_3$ ): 2.04(3H,s); 3.03(3H,s); 3.13(3H,s); 3.7-4.1 (1H,broad, $\text{D}_2\text{O}$  exch.); 3.84(1H,1/2ABq,J=12Hz); 4.01(1H,1/2ABq,J=17Hz); 4.12(1H,1/2ABq,J=17Hz); 4.33(1H,1/2ABq,J=12Hz)

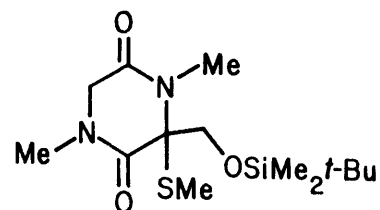
IR: 3420,3330,1640,1660,1450,1395

Mass Spectrum: 187(1.05); 171(25.6); 142(30); 42(100)

Anal. calcd. for  $\text{C}_8\text{H}_{14}\text{N}_2\text{O}_3\text{S}$ : C,44.02; H,6.46;N,12.83;S,14.69

found: C,43.89; H,6.56;N,12.71;S,14.75

1,4-dimethyl-3-(*t*-butyldimethylsiloxy)  
methyl-3-methylthio-2,5-piperazine-  
dione (214)



tert-butyldimethylsilyl chloride  
(1.7151g, 11.38mmol, 1.2eq), imidazole  
(1.5522g, 22.8mmol, 2.4eq) and alcohol  
(213) (3.07g, 9.5mmol, 1.0eq) were stirred in 9mL DMF at  
room temperature for 12 hours. The solution was diluted  
with CH<sub>2</sub>Cl<sub>2</sub>, poured into 0.25 N HCl and extracted with  
CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium  
sulfate, filtered and evaporated, affording 3.19g (100%) of  
pure, oily silyl ether 214.

NMR(A) (CDCl<sub>3</sub>) δ TMS (external): 0.07 (3H, s); 0.10 (3H, s);  
0.88 (9H, s); 2.05 (3H, s); 3.05 (3H, s); 3.14 (3H, s);  
3.80 (1H, 1/2ABq, J=10Hz); 4.07 (2H, s); 4.32 (1H,  
1/2ABq, J=10Hz).

IR (neat, NaCl): 1670, 1395, 1260, 1210

Mass Spectrum: 332 (M<sup>+</sup>, 0.14), 317 (0.68), 285 (25.6),  
275 (23.9), 228 (55.8), 73 (100)

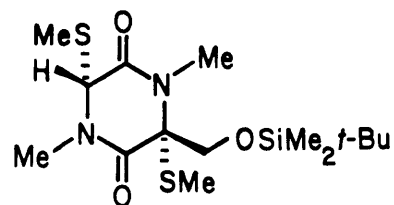


1,4-dimethyl-3-(*t*-butyldimethylsiloxy)

methyl-3-methylthio-6-methylthio-

2,5-piperazinedione (215)

A solution of 214 (0.7615g, 2.29mmol, 1.0eq) in 22mL THF was cooled to -78°C.



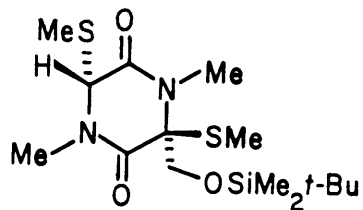
To this stirred solution was added LDA

(2.75mmol, 1.2eq) in 3mL THF dropwise via cannula. After stirring the dark colored solution for 1 minute at -78°C, the mixture was added to a stirred solution of methyldisulfide in 5mL THF at -78°C via cannula. After stirring 5 minutes at -78°C, the mixture was allowed to come to 0°C and was quenched with 3mL of 1N HCl. The mixture was then poured into 0.1N HCl and the aqueous layer was thoroughly extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated, and separated on preparative silica gel TLC (eluted with ethylacetate) to afford 0.4338g (50%, 66% based on recovered 214, 0.1851g) 215 as an oil.

NMR(D) (CDCl<sub>3</sub>)δTMS(external) 0.05(3H,s); 0.08(3H,s); 0.85(9H,s);  
 2.20(3H,s); 2.43(3H,s); 3.13(3H,s); 3.15(3H,s);  
 3.85(1H,1/2ABq,J=10Hz); 4.35(1H,1/2ABq,J=10Hz);  
 4.70(1H,s).

IR: 1660, 1260, 1120, 1105, 830.

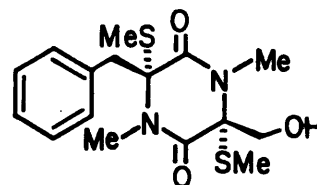
Mass spectrum:  $m/e = 331.14860$   $(M-SCH_3)^+ C_{14}H_{27}N_2O_3SiS$   
 requires 331.15117;  $321.07697$   $(M-C_4H_9)^+ C_{11}H_{21}N_2O_3SiS_2$   
 requires 321.07630.



NMR(D) (CDCl<sub>3</sub>) δ TMS (external: 0.09 (3H, s); 0.13 (3H, s);  
 0.93 (9H, s); 2.04 (3H, s); 2.23 (3H, s); 3.20 (6H, s);  
 3.85 (1H, 1/2ABq, J=10Hz); 4.43 (1H, 1/2ABq, J=10Hz);  
 4.92 (1H, s).

(+)-gliovictin(52)

To a stirred solution of diastereomers 215 (1.0051g, 2.65mmol, 1.0eq) in 25mL THF at -78°C was added a solution of LDA (3.3mmol, 1.25eq) in 3.5mL THF. After stirring the dark enolate solution for 2 minutes at -78°C, benzyl bromide (1.57mL, 13.25mmol, 5.0eq) was added. The mixture was allowed to come to room temperature, stirred an additional 15 minutes and quenched with enough 1N HCl to turn the dark solution clear and colorless. The mixture was poured into 0.1N HCl and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The residue was dissolved in 50mL of 2N HCl in MeOH with a few drops of water, and stirred for 6 hours at room temperature. The solution was poured into a saturated sodium chloride solution and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on a silica gel flash chromatographic column (eluted with EtOAc) to afford 0.7918g (85%) (+)-gliovictin 52 as white crystals mp 118-120°C.



NMR(D) (CDCl<sub>3</sub>): 1.54(1H,exch.,broad unsym. triplet,

$J_{ax}=7\text{Hz}$ ,  $J_{bx}=7.5\text{Hz}$ ); 2.14(3H,s); 2.31(3H,s); 3.04(3H,s);

3.29(3H,s); 3.15(1H,1/2ABq, $J=14\text{Hz}$ ); 3.75(1H,1/2ABq, $J=14\text{Hz}$ );

3.14 (1H, dd,  $J_{ax}=7\text{Hz}$ ,  $J_{ab}=12\text{Hz}$ ); 3.85 (1H, dd,  $J_{bx}=7.5\text{Hz}$ ,  $J_{ab}=12\text{Hz}$ ); 7.08-7.4 (5H, m).

IR: 3380, 1660, 1636, 1499, 1373, 735, 700.

Anal. calcd. for  $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_3\text{S}_2$ : C, 62.5; H, 6.25; N, 7.90; S, 18.09,  
found : C, 54.28; H, 6.31; N, 7.69; S,  
S, 18.31.

Mass Spectrum: M-1 at 353 (weak),  $m/e = 323.08629$

( $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_2\text{S}_2$ , requires 323.08880)

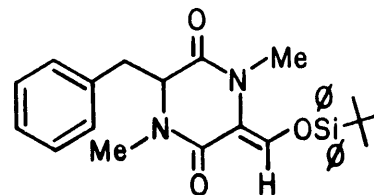
$m/e = 307.11066$

( $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$ , requires 307.11164).

\*Note - Analysis of the crude reaction mixture, after hydrolysis of the silyl protecting group, by HPLC (porasil,  $\text{CH}_2\text{Cl}_2/\text{EtOAc}$  1:1) revealed that less than 10% of diastereomeric material (epi-gliovictin 221) was present.

1,4-dimethyl-3-(t-butyl-diphenylsiloxy)-  
formyl-6-benzyl-2,5-piperazinedione (**217**)

A solution of **211** (24.25g, 59.4mmol, 1.0eq) in 200mL THF was cooled in a dry ice-ether bath. A solution of LDA



(62.37mmol, 1.05eq) in 40mL THF was added dropwise with stirring. After stirring 5 min. at  $-78^{\circ}\text{C}$ , the orange enolate solution was transferred via cannula to a solution of benzyl bromide (35mL, 297mmol, 5.0eq) in 50 mL THF at  $-78^{\circ}\text{C}$ . The resulting light yellow solution was stirred 20 min. at  $-78^{\circ}\text{C}$  and allowed to warm to room temperature. The solvent was evaporated and the oily residue was triturated with pentane until a powdery precipitate formed. The solid was filtered, washed with pentane and partitioned between pH 7.0 buffer and  $\text{CH}_2\text{Cl}_2$ . The aqueous layer was thoroughly extracted with  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated, affording 23.75g (80.2%) **217** as white crystals mp  $148.5\text{--}150^{\circ}\text{C}$  (recryst. EtOAc).

\*Note - higher yields (up to 97%) could be realized when the reaction was run on smaller scales, the product separated by chromatography, and/or product retrieved from the mother liquors of the pentane trituration.

NMR(D) ( $\text{CDCl}_3$ ): 1.13(9H,s); 2.80(3H,s); 3.12(2H,d,J=6 Hz.); 3.43(3H,s); 4.20(1H,t,J=6 Hz.); 6.83(1H,s); 7.20(5H,m); 7.35-7.75(10H,m).

IR: 1745, 1670, 1625, 1585, 1210, 1200, 1150, 1110, 780, 750, 715, 700

Anal. calcd. for  $C_{30}H_{34}N_2O_3Si$ : C, 72.25; H, 6.87; N, 5.62

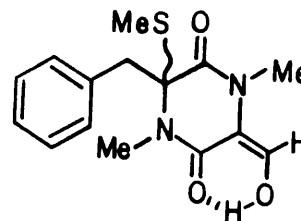
found: C, 72.12; H, 7.14; N, 5.58

Mass Spectrum: calcd. for  $C_{30}H_{34}N_2O_3Si$ : 498.23387

found: 498.23284

1,4-dimethyl-3-formyl-6-methylthio-6-benzyl-2,5-piperazinedione (218)

To a stirred solution of 217 (4.00g, 8.0mmol, 1.0eq) in 60mL THF at -78°C was added a solution of LDA (9.23mmol, 1.15eq) in 10mL THF. The resulting dark-colored enolate solution was allowed to stir at -78°C for 3 minutes and was then transferred, via cannula, into a solution of methyl disulfide in 40mL THF at -100°C. The resulting pale orange solution was stirred 1 hour at -100°C and was then allowed to warm to room temperature. The reaction was quenched with 10mL of 0.65 N HCl in MeOH. The mixture was poured into pH 7.0 buffer and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on a silica gel column (eluted with 2% methanol in methylene chloride) to give 2.0058g (82%) 218 as an air sensitive oil (must be used immediately after preparation).



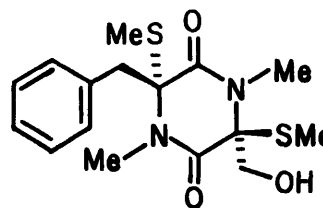
NMR(A) (CDCl<sub>3</sub>): 1.97(3H,s); 2.98(3H,s); 3.18(3H,s); 3.04(1H,1/2 ABq,J=14Hz); 3.63(1H,1/2ABq,J=14Hz); 6.68(1H,d,J=11Hz); 7.1(5H,m); 12.18(1H,d,J=11Hz,D<sub>2</sub>O exch.)

IR(Neat,NaCl): 3650-3200(broad),1650,1595,1385,1240,1185,1135, 850,700

Mass spectrum: 306(M<sup>+</sup>,0.55); 275(6.79); 259(4.66); 91(100).

(+)-epi-gliovictin (221)

To a stirred solution of 218 (0.4602g, 1.5mmol, 1.0eq) in 5mL THF at -100°C was added  $\text{Et}_3\text{N}$  (0.26mL, 1.87mmol, 1.25eq). To this solution was added  $\text{CH}_3\text{SCl}$  (0.1544g, 1.87mmol, 1.25eq) in 3mL THF. After stirring 30 minutes at -100°C, the white suspension was warmed to 0°C and filtered to remove  $\text{Et}_3\text{N HCl}$ . Evaporation of the solvent afforded oily 220, which by NMR analysis, was a 3:1 (anti:syn) mixture of diastereomers. This oily residue was dissolved in 5mL THF and cooled to -78°C. To this solution was added  $\text{LiAl}(\text{tert-BuO})_3\text{H}$  (0.7628g, 3.0mmol, 2.0eq) in 10mL THF. After stirring 30 minutes at -78°C, the mixture was allowed to come to room temperature and stirred an additional 2 hours. The reaction was quenched with 1N HCl in MeOH, poured into 5% HCl and extracted thoroughly with  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel TLC (eluted with 27  $\text{CH}_2\text{Cl}_2$  : 3EtOAc:1 MeOH) to afford (+)-gliovictin 53 0.0831g (15.6%) and (+)-epi-gliovictin 221 0.2161g (40.6%) as white crystals mp 163-165.5°C (recryst  $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ ).



NMR(D) ( $\text{CDCl}_3$ ): 1.13(3H,s); 2.14(3H,s); 3.06(3H,s); 3.15(1H, exch.,broad s); 3.29(3H,s); 3.20(1H,1/2ABq, J=15Hz); 3.74(1H,1/2ABq,J=12Hz); 3.83(1H,1/2 ABq,J=15Hz); 4.16(1H,1/2ABq,J=12Hz);



IR: 3465, 3400, 1665, 1635, 1499, 1380, 755, 700

Anal. calcd. for  $C_{16}H_{22}N_2O_3S_2$ : C, 54.21; H, 6.25; N, 7.90;  
S, 18.09;

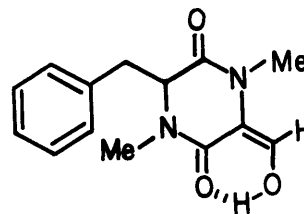
found: C, 54.21; H, 6.33; N, 7.81;  
S, 17.93.

Mass Spectrum:  $m/e = 323.08844$  ( $C_{15}H_{19}N_2O_2S_2$ ,  
requires: 323.08880

$m/e = 307.11344$  ( $C_{15}H_{19}N_2O_3S$ ,  
requires 307.11164.

\* see separate experimental for spectral data on 53.

1,4-dimethyl-3-formyl-6-benzyl-2,5-piperazinedione 223



To a stirred solution of 217 (0.4199g, 0.84mmol, 1.0eq) in 3mL methanol was added potassium fluoride (0.0976g, 1.68mmol, 3.0eq) at room temperature. After stirring the mixture for 15 minutes, 1mL of 3% HCL in MeOH was added. The solvent was evaporated and tert-butyldiphenylsilyl fluoride was triturated away from the solid residue with hexanes. the resulting methylene chloride soluble residue afforded 0.1697g (92%) of enol 223 as white crystals mp 106-109°C (recryst. CH<sub>2</sub>Cl<sub>2</sub>).

NMR(A) (CDCl<sub>3</sub>): 2.85(3H,s); 3.04(3H,s); 3.13(2H,d,J=6Hz); 4.27(1H,t,J=6Hz); 6.43(1H,d,J=11.5Hz); 6.807.4(5H,m); 11.9(1H,exch.,d,J=11.5)Hz).

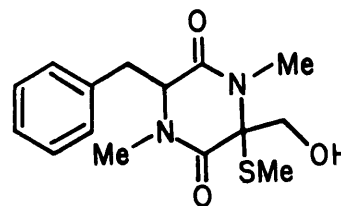
IR: 3460 (broad), 1660, 1620, 1510, 1485, 1225, 1140, 900, 755, 710

Mass Spectrum: Calculated for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: 260.11609

Found: 260.11843

1,4-dimethyl-3-hydroxymethyl-3-methylthio-  
6-benzyl-2,5-piperazinedione (225)

To a stirred solution of enol 223 (0.8724g, 3.35mmol, 1.0eq) in 10mL THF at -78°C was added triethylamine (0.58mL, 4.18mmol, 1.25eq). To this solution was added methylsulphenyl chloride (0.3457g, 4.18mmol, 1.25eq) in 4mL THF. The resulting white suspension was stirred 10 minutes at -78°C, warmed to 0°C, filtered and evaporated to afford a 3:1 mixture of syn:anti diastereomeric aldehydes 224 (NMR analysis). This mixture was redissolved in 20mL THF at -78°C and a solution of lithium tri-*t*-butoxyaluminum hydride (1.0647g, 4.18mmol, 1.25eq) in 10mL THF was slowly added. The mixture was stirred 1 hour at -78°C, warmed to room temperature and acidified with 0.65N HCl in MeOH. The solvents were evaporated and the residue triturated with CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> soluble portion was separated on preparative silica gel TLC (eluted with 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to afford 0.3307g (32%) of the syn isomer 225 and 0.1754g (17%) of the anti isomer 225.



syn isomer:

NMR(A) (CDCl<sub>3</sub>): 1.82(3H,s); 2.90(3H,s); 2.84(1H,1/2ABq,J=11Hz);  
2.98(3H,s); 3.20(2H,d,J=4Hz); 3.49(1H,1/2ABq,J=11Hz);  
4.23(1H,t,J=4Hz); 7.05(5H,m).

IR: 3380(broad); 1650,1625,1495,1450,1385,1060,755,705.

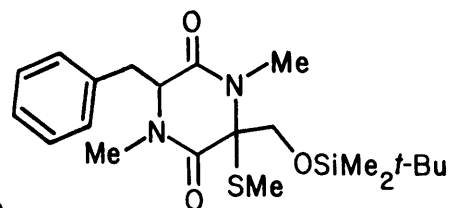
Mass Spectrum: 277(1.42); 261(31.65); 91(16.8); 42(100).

anti isomer:

NMR(A) (CDCl<sub>3</sub>): 1.80 (3H, s); 2.68 (3H, s); 3.05 (3H, s);  
3.2-4.5 (6H, m); 7.15 (5H, s).

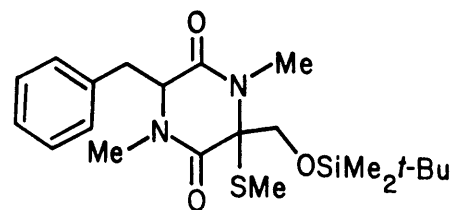
silylether 226 from alcohol 225

syn-Alcohol 225 (0.3307g,  
1.07mmol, 1.0eq), tert-butyldimethyl-  
silylchloride (0.202g, 1.34mmol, 1.25eq)  
and imidazole (0.1824g, 2.86mmol, 2.5eq)



were stirred in 0.5mL DMF at room temperature 12 hours. The  
resulting solution was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with 0.5N  
HCl, aqueous sodium bicarbonate, dried over anhydrous sodium  
sulfate, filtered and evaporated to afford 0.3925g (86%) of  
silyl ether 225 which was identical to that obtained from  
214 (see separate preparation for spectral data).

1,4-dimethyl-3-(t-butyldimethylsiloxy)-  
3-methylthio-6-benzyl-2,5-piperazine-  
dione (226)



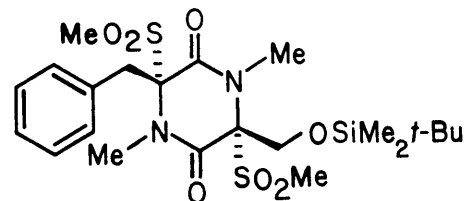
To a stirred solution of 214  
(0.7140g, 2.12mmol, 1.0eq) in 18mL  
THF at -78°C was added a solution of  
LDA (2.64mmol, 1.25eq) in 2mL THF. The dark-colored enolate  
solution was stirred 30 seconds at -78°C and benzyl bromide  
(1.26mL, 10.6mmol, 5.0eq) was added dropwise. After stirring  
3 minutes at -78°C, the cooling bath was removed and the  
mixture allowed to warm to 0°C. The green-colored solution was  
quenched with 3mL of 1N HCl, poured into 0.1N HCl and extracted  
thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over  
anhydrous sodium sulfate, filtered, evaporated and separated  
on preparative silica gel TLC (eluted with 50% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>)  
to afford 0.4469g (76.6%) of 226 as a glass.

NMR(D) (CDCl<sub>3</sub>): 0.03(3H,s); 0.06(3H,s); 0.92(9H,s); 1.90(3H,s);  
2.92(3H,s); 3.12(3H,s); 3.15-3.4(3H,m); 3.78(1H,d,J=10Hz);  
4.32(1H,t,J=5Hz); 7.1-7.4(5H,m).

IR: 1650,1395,1255,1120,840,780,750,700.

Mass Spectrum: 375(34.07); 365(9.53); 227(27.43); 91(26.43);  
40(100).

1,4-dimethyl-3-(t-butyldimethylsiloxy)  
methyl-6-benzyl-3,6-dimethylsulfone-  
2,5-piperazinedione (228)



Gliovictin (52) (0.0758g, 0.21mmol, 1.0eq), tert-butyldimethylsilyl chloride (0.0387g, 0.26mmol, 1.2eq) and imidazole (0.0354g, 0.52mmol, 2.4eq) were stirred in 0.4mL DMF at room temperature for 12 hours. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with 0.1N HCl. The organic extract was dried over anhydrous sodium sulfate, filtered and evaporated. The oily residue was dissolved in 3mL CHCl<sub>3</sub> and m-CPBA (0.2545g, 1.26 mmol, 6.0eq) was added portionwise. The mixture was stirred for 12 days at room temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with a saturated sodium bicarbonate solution. The organic extract was dried over anhydrous sodium sulfate, filtered and evaporated to afford 0.1103g (99%) of bismethylsulfone 228 as a glass.

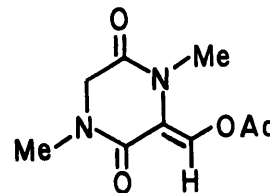
NMR(A) (CDCl<sub>3</sub>): 0.00(3H,s); 0.15(3H,s); 0.95(9H,s); 3.35(3H,s); 3.44(3H,s); 3.46(3H,s); 3.50(3H,s); 3.97(1H,1/2 ABq, J=15Hz); 4.22(1H,1/2ABq,J=15Hz); 4.47(1H, 1/2ABq,J=11Hz); 4.66(1H,1/2ABq,J=11Hz); 7.40 (5H,s).

IR(NaCl,neat): 1680,1500,1370,1305,1255,1140,1120,980,840,750, 700.

Mass Spectrum: 453(3.37); 373(16.44); 317(30.64); 73(100).

Pummerer reaction of 214

Silyl ether 214 (0.1889g, 0.57mmol, 1.0eq) was dissolved in 1mL CH<sub>2</sub>Cl<sub>2</sub> and m-CPBA (0.1377g, 0.68mmol, 1.2eq) was added portionwise. The mixture was stirred at room temperature 12 hours, diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and evaporated. The resulting oily residue was dissolved in 5mL acetic anhydride and refluxed for 15 hours. Evaporation of the solvent afforded 0.1139g (94%) of enolacetate 231 as glass.

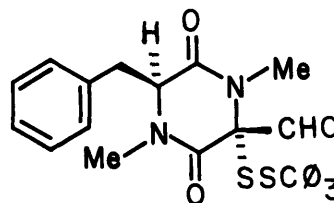


NMR(A) (CDCl<sub>3</sub>): 2.25 (3H,s); 3.00 (3H,s); 3.35 (3H,s);  
4.02 (2H,s), 7.87(1H,s)

IR(NaCl, neat): 1820, 1780, 1695, 1640, 1200, 1140, 750.

Mass Spectrum: 212(M<sup>+</sup>,0.78); 170(10.31); 42(100)

1,4-dimethyl-3-(trityldithio)-3-carboxaldehyde-6-benzyl-2,5-piperazinedione (235)



To a stirred solution of 223 (0.9879g, 3.79mmol, 1.0eq) in 10mL THF at  $-78^{\circ}\text{C}$  was added triethylamine (0.56mL, 3.98mmol, 1.05eq). To this solution was added a solution of triphenylmethyl chlorodisulfide (1.366g, 3.98mmol, 1.05eq) in 10mL THF. After addition, the resulting white suspension was stirred 10 minutes at  $-78^{\circ}\text{C}$ , warmed to  $0^{\circ}\text{C}$ , filtered and evaporated to afford 2.137g (99.4%) of disulfide aldehyde 235 as a brittle white foam.

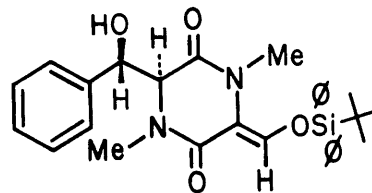
NMR(D) ( $\text{CDCl}_3$ ): 2.57(3H,s); 2.84(3H,s); 3.13(2H,m); 4.10(1H,t,J=4Hz); 6.8-7.5(20H,m); 7.90(1H,s).

IR: 1735,1670,1495,1445,1390,750,700.

Mass Spectrum: 375(41.47); 290(0.62); 261(2.77); 243(1.41); 227 (35.55); 91(31.09); 73(100).



1,4-dimethyl-3-(tert-butyldiphenyl-  
siloxy)formyl-6-(benzylcarbinol)-  
2,5-piperazinedione (240)



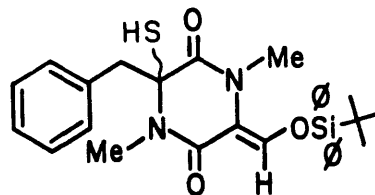
To a stirred solution of 211  
(0.4086g, 1.0mmol, 1.0eq) in 10mL THF  
at -78°C was added a solution of LDA  
(1.15mmol, 1.15eq) in 2mL THF. After stirring the orange-  
colored enolate solution for 3 minutes at -78°C, benzaldehyde  
(0.3mL, 3.0mmol, 3.0eq) was added and stirring continued for  
15 minutes at -78°C and 1 hour at room temperature. The mixture  
was acidified with 2N HCl, poured into water and extracted  
thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over  
anhydrous sodium sulfate, filtered, and evaporated to afford  
0.3808g (74%) of alcohol 240 as white crystals mp 152-154°C  
(recryst CH<sub>2</sub>Cl<sub>2</sub>).

NMR(A) (CDCl<sub>3</sub>): 1.10(9H,s); 2.74(3H,s); 3.37(3H,s); 4.19(1H,d,  
J=4Hz); 4.6(1H,broad s, exch.); 5.05(1H,d,J=4Hz);  
6.82(1H,s); 7.0-7.9(15H,m).

IR: 3400(broad); 1665,1600,1420,1200,1160,775,710,700.

Mass Spectrum: 408(23.25); 351(26.89); 106(23.81), 45(100).

1,4-dimethyl-3-(tert-butyldiphenylsioxly)  
formyl-6-mercapto-6-benzyl-  
2,5-piperazinedione (243)



To a stirred solution of 217 (3.50g, 7.0mmol, 1.0eq) in 60mL THF at  $-78^{\circ}\text{C}$  was added a solution of LDA (8.0mmol, 1.15eq) in 7mL THF. The resulting dark colored enolate solution was stirred 30 seconds at  $-78^{\circ}\text{C}$  and added, via cannula, to a solution of elemental sulfur (0.4582g, 14.0mmol, 2.0eq) in 80mL THF at  $-78^{\circ}\text{C}$ . The mixture was stirred 20 minutes at  $-78^{\circ}\text{C}$ , quenched with 20mL of 0.65 N  $\text{NCl}$  in MeOH, warmed to room temperature, poured into 0.1 N  $\text{HCl}$  and extracted thoroughly with  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The crude mercaptan was dissolved in 30mL EtOH + 10mL THF at  $0^{\circ}\text{C}$  and  $\text{NaBH}_4$  (1.2737g, 33.7mmol, 4.8eq) was added portionwise. The mixture was stirred 10 minutes at  $0^{\circ}\text{C}$ , quenched with 0.1 N  $\text{HCl}$  and extracted thoroughly with  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated to afford 3.7168g (99%) 243 as brittle, white foam.

$\text{NMR(D)} (\text{CDCl}_3)$ : 1.10(9H,s); 3.07(3H,s); 3.22(1H,s); 3.37(1H, 1/2ABq,  $J=14\text{Hz}$ ); 3.51(3H,s); 3.87(1H, 1/2ABq,  $J=14\text{Hz}$ ); 6.94(1H,s); 6.98–7.35(5H,m), 7.35–7.8(10H,m).

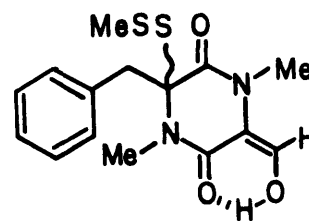
IR: 2550, 1675, 1620, 1495, 1390, 1360, 1185, 1160, 1110, 745, 700

Mass Spectrum: 531( $\text{M}^+$ 1.09), 498(1.19), 135(100), 91(66).

1,4-dimethyl-3-formyl-6-benzyl-6-

(methyldisulfide)-2-5,piperazinedione (246)

To a stirred solution of thiol 243 (1.122g, 2.1mmol, 1.0eq) in 5mL THF at -78°C was added triethylamine (0.32mL, 2.31mmol, 1.1eq) and a solution of freshly prepared methylsulphenyl chloride (0.227g, 2.75mmol, 1.3eq) in 5mL THF. The resulting white suspension was stirred 20 minutes at -78°C, 20 minutes at room temperature, filtered to remove Et<sub>3</sub>N·HCl and the solvent evaporated to afford disulfide 245 as a brittle, pale yellow foam. Without further purification, 245 was dissolved in 10mL THF, 20mL 1.6N HCl in MeOH, 3mL 6N HCl and stirred at room temperature 18 hours. The solution was poured in water and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on a silica gel flash column (eluted with CH<sub>2</sub>Cl<sub>2</sub>) to afford 0.362g (51%) of enolic disulfide 246 as an oil.



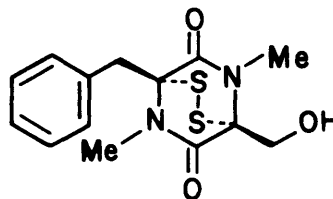
NMR(A) (CDCl<sub>3</sub>): 2.30 (3H,s); 3.08 (1H,1/2ABq,J=14Hz); 3.07 (3H,s)  
3.09 (3H,s); 3.89 (1H,1/2ABq,J=14Hz); 6.90 (1H,d,J=12Hz);  
7.18 (5H,m); 12.41 (1H,exch.d,J=12Hz).

IR: (NaCl,neat): 1660, 1605, 1500, 1420, 1395, 1250, 1195, 1145,  
750, 705.

Mass Spectrum: 337(0.42); 292(0.36); 259(25.06); 91(89.42);  
42(100).

(+)-hyalodendrin(53) from 246

To a stirred solution of enolic methyldisulfide 246 (0.3516g, 1.04mmol, 1.0eq) in 10mL THF at -78°C was added triethylamine (0.15mL, 1.04mmol, 1.0eq).



To this solution was added triphenylmethyl chlorodisulfide in 5mL THF over a 3 minute period. The resulting white suspension was stirred 20 minutes at -78°C, warmed to room temperature, filtered and the solvent evaporated to afford 0.6762g (100%) of aldehyde 247 as a brittle foam. Analysis of 247 by  $^1\text{H}$  NMR indicated a ca. 2:1 anti:syn ratio of diastereomers (anti aldehyde proton at  $\delta$ 8.2; syn proton at  $\delta$ 7.8).

To a stirred solution of diastereomers 247 (0.3272g, 0.51mmol, 1.0eq) in 5mL THF at 0°C was added sodium borohydride (0.1342g, 3.55mmol, 7.0eq). After stirring 3 minutes at 0°C, 1mL of isopropanol was added. The mixture was warmed to room temperature, stirred 30 minutes, and then refluxed for 30 min. Stirring was continued for 1 hour at room temperature and an additional 7.0eq of sodium borohydride was added. The mixture was refluxed for 30 minutes and then stirred at room temperature 12 hours. The mixture was acidified with 1N HCl, saturated with NaCl and extracted thoroughly with  $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The residue was dissolved in 20mL isopropanol + 10mL THF at 0°C and sodium borohydride was added (0.1342g, 3.55mmol, 7.0eq). The mixture was warmed to room temperature, stirred 12 hours, acidified and extracted as above. The residue was dissolved

in 15mL  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  and a 2.5% solution of  $\text{KI}_3$  in pyridine was added dropwise until a faint iodine color persisted. The solution was filtered and the  $\text{CH}_2\text{Cl}_2$  soluble residue was separated on preparative silica gel TLC (eluted with 2% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to afford 0.0486g (29.4%) of (+)-hyalodendrin (53) as pale yellow crystals mp  $128\text{--}131^\circ\text{C}$  (recryst  $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ ).

NMR(E) ( $\text{CDCl}_3$ ): 3.04 (3H, s); 3.26 (3H, s); 3.60 (1H, exch. dd,  $J_{\text{AX}}=7.2\text{Hz}$ ,  $J_{\text{BX}}=8.9\text{Hz}$ ); 3.69 (1H, 1/2ABq,  $J=16\text{Hz}$ ); 4.13 (1H, 1/2ABq,  $J=16\text{Hz}$ ); 4.33 (1H, dd,  $J_{\text{AB}}=14\text{Hz}$ ,  $J_{\text{AX}}=7.2\text{Hz}$ ); 4.40 (1H, dd,  $J_{\text{AB}}=14\text{Hz}$ ,  $J_{\text{BX}}=8.9\text{Hz}$ ); 7.35 (5H, s).

IR: 3500 (broad); 1695, 1670, 1500, 1458, 1423, 1360, 1255, 1245, 1220, 1085, 770, 718, 710.

Mass Spectrum: 324 ( $\text{M}^+$ , 1.15); 259 (45.92); 231 (16.02); 214 (18.41); 91 (72.51); 42 (100).

Accurate mass measurements:

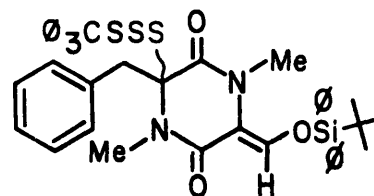
Calcd. for  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3\text{S}_2$  ( $\text{M}^+$ ): 324.06024  
found: 324.06096

Calcd. for  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$  ( $\text{M}-\text{S}_2$ ) $^+$ : 260.11609  
found: 260.11543

Anal. calcd. for  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3\text{S}_2$ : C, 51.83; H, 4.97; N, 8.63;  
S, 19.76.  
found: C, 52.26; H, 4.98; N, 8.23;  
S, 19.44.

1,4-dimethyl-3-(tert-butyldiphenylsiloxy)  
formyl-6-benzyl-6-(tritylsulfide)-  
2,5-piperazinedione (248)

To a stirred solution of thiol 243 (0.5307g, 1.0mmol, 1.0eq) in 5mL THF at -78°C was added triethylamine (0.14mL, 1.0mmol, 1.0eq). To this solution was added a solution of triphenylmethyl chlorodisulfide (0.3429g, 1.0mmol, 1.0eq) in 5mL THF. The mixture was stirred at -78°C for 15 minutes, warmed to 0°C, filtered and evaporated. The oily residue was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with 0.1N HCl. The organic extract was dried over anhydrous sodium sulfate, filtered and evaporated to afford 0.5782g (69%) of trisulfide 248 as white crystals mp 172-174°C (recryst CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O).



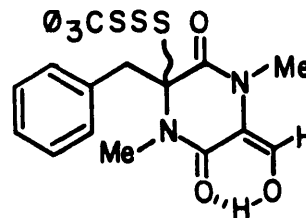
NMR(A) (CDCl<sub>3</sub>): 1.05(9H,s); 2.90(3H,s); 2.89(1H,1/2ABq,J=14Hz);  
3.50(3H,s); 3.76(1H,1/2ABq,J=14Hz); 7.0-7.7(30H,m).

IR: 1675,1660,1612,1335,1175,1155,735,700.

Mass Spectrum: 495(2.48); 438(14.39); 243(100); 164(99.4)

1,4-dimethyl-3-formyl-6-benzyl-6-(tri-  
tyltrisulfide)-2,5-piperazinedione (249)

Silylenolether 248 (0.50g, 0.6mmol)  
was dissolved in 20mL THF, 10mL  $\text{CHCl}_3$ ,  
20mL of 1.6M HCl in MeOH and 2mL of  
6N HCl at room temperature. The mixture



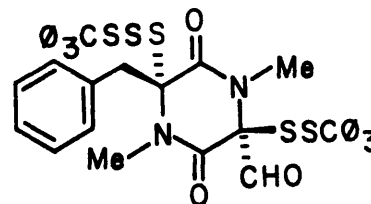
was stirred for 6 hours, poured into water and extracted with  
 $\text{CH}_2\text{Cl}_2$ . The combined extracts were dried over anhydrous sodium  
sulfate, filtered, evaporated and separated on a silica gel flash  
column (eluted with  $\text{CH}_2\text{Cl}_2$ ) to afford 0.1765g (49%) of enolic  
trisulfide 249 as white crystals mp 150-152°C (recryst  $\text{CH}_2\text{Cl}_2$ /  
 $\text{Et}_2\text{O}$ ).

NMR(A) ( $\text{CDCl}_3$ ): 2.92(6H,s); 2.86(1H,1/2ABq,J=14Hz);  
3.70(1H,1/2ABq,J=14Hz); 6.78(1H,d,J=11Hz);  
6.9-7.4(20H,m); 12.28(1H,exch.,d,J=11Hz).

IR: 3460 (broad), 1650, 1590, 1485, 1385, 1240, 1190, 1135, 745,  
730, 695.

Mass Spectrum: 258(12.7); 243(60.64); 165(100); 91(56.68).

1,4-dimethyl-3-(trityldisulfide)-  
3-carboxaldehyde-6-benzyl-6-(trityl-  
trisulfide)-2,5-piperazinedione (250)



To a stirred solution of 249  
(0.7274g, 1.2mmol, 1.0eq) in 10mL THF  
at -78°C was added triethylamine (0.17mL,  
1.2mmol, 1.0eq). To this solution was added triphenylmethyl  
chlorodisulfide (0.4171g, 1.2mmol, 1.0eq) in 5mL THF. The  
resulting white suspension was stirred for 1 hour at -78°C,  
warmed to room temperature, filtered and evaporated to afford  
1.1727g (quant.) 250 as a brittle, white foam.

NMR(A) (CDCl<sub>3</sub>): 2.60(3H,s); 2.90(3H,s); 2.94(1H,1/2ABq,J=14Hz);  
3.25(1H,1/2ABq,J=14Hz); 7.22(35H,s); 8.19(1H,s).

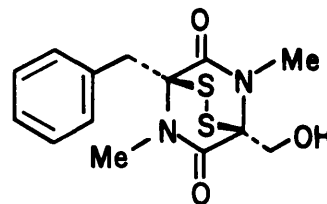
IR: 1730,1675,1665,1600,1495,1445,1370,740,705.

Mass Spectrum: 439(0.34); 257(18.92); 242(66.24); 165(100).



(+)-hyalodendrin (53) from 250.

Sodium borohydride (0.2011g, 5.32mmol, 7.0eq) was added portionwise to a stirred solution of 250 (0.687g, 0.76mmol, 1.0eq) in 6mL of DME at room temperature. After stirring 1 minute, 1mL of isopropanol was added and the mixture was refluxed for 30 minutes. An additional 5mL DME, 3mL isopropanol and 7.0eq of sodium borohydride was added and the mixture was refluxed for 1 hour and then stirred 1 hour at room temperature. The mixture was acidified with 1N HCl and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were placed in a separatory funnel with water and a 10% solution of KI<sub>3</sub> in water was added dropwise with subsequent shaking until the faint color of iodine persisted. The aqueous phase was extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were dried over anhydrous sodium sulfate, filtered and evaporated. Analysis of the residue by TLC indicated the absence of hyalodendrin product. Re-reduction of this residue with 0.2011g (7.0eq, 5.32mmol) of sodium borohydride in 5mL DME + 5mL isopropanol at room temperature for 36 hours afforded after acidification and oxidation as described above, and separation of the residue on preparative silica gel TLC, 7.0mg (2.8%) of (+)-hyalodendrin (53) that was identical to that obtained from 247 (see experimental).

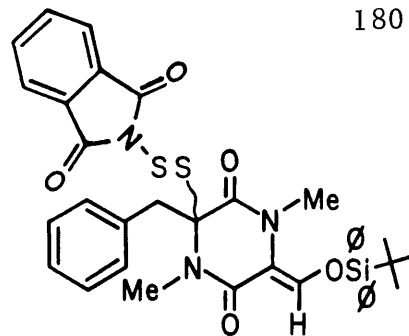


Reductive methylation of 250

To a stirred solution of 250 (0.1308g, 0.14mmol, 1.0eq) in 0.23mL pyridine and 1.1mL methyl iodide at 0°C was added an ice-cold solution of sodium borohydride (0.0378g, 1.0mmol, 7.0eq) in 1.1mL methanol. The mixture was allowed to stir 1 hour at 0°C and 4 hours at room temperature. The solvents were evaporated and the residue was partitioned between water and CH<sub>2</sub>Cl<sub>2</sub>. The aqueous layer was acidified with 1N HCl to pH=3 and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated. Analysis of the crude product by HPLC (porasil, CH<sub>2</sub>Cl<sub>2</sub>:EtOAc, 1:1) revealed that the ratio of epi-gliovictin (221) to gliovictin (53) was greater than 10:1. This was confirmed by coinjection with authentic samples of 221 and 52. Analysis by TLC (eluted with 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub>, silica gel) confirmed (approximately) the ratio determined by HPLC.

To a stirred solution of 250 (0.5135g, 0.57mmol, 1.0eq) in 10mL THF at 0°C was added sodium borohydride (0.1503g, 3.97mmol, 7.0eq) portionwise. The mixture was stirred 3 minutes and 2mL i-PrOH was added. The solution was refluxed for 1 hour and stirred at room temperature for 12 hours. An additional 7.0eq of sodium borohydride was added and stirring was continued for 12 hours at room temperature. The mixture was acidified with 1N HCl, saturated with sodium chloride and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The residue was dissolved in 1mL pyridine at 0°C and 5mL of methyl iodide was added. An ice cold solution of sodium borohydride (0.10g) in 1mL methanol was added and the mixture stirred 30 minutes at 0°C. An additional 1mL of methyl iodide was added and stirring continued for 3 hours at room temperature. The solvents were evaporated and the residue was partitioned between water and CH<sub>2</sub>Cl<sub>2</sub>. The pH of the aqueous phase was adjusted to 6 with 1N HCl and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated. Analysis of the residue by HPLC (porasil, 1:1 CH<sub>2</sub>Cl<sub>2</sub>/EtOAc) indicated an approximately 50:50 mixture of gliovictin (52) and epi-gliovictin (221). Separation of the residue on preparative silica gel TLC (eluted with 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) afforded 0.0293g (14.5%) gliovictin (52) and 0.0411g (20.4%) of epi-gliovictin (see separate experimentals for spectral data).

1,4-dimethyl-3-(tert-butyldiphenylsiloxy)  
formyl-6-benzyl-6-(phthalimidodisulfide)-  
2,5-piperazinedione (259)



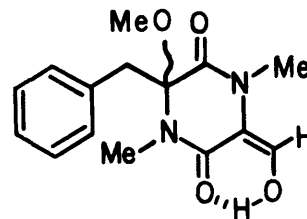
To a stirred solution of N,N'-thio-bisphthalimide <sup>110,119</sup> (0.7783g, 2.4mmol, 1.2eq) in 23mL methylene chloride at reflux was added a solution of 243 (1.0614g, 2.0mmol, 1.0eq) in 7mL THF. The mixture was refluxed 1 hour, cooled and the solvent evaporated. The residue was triturated with THF, filtered and the solvent removed under reduced pressure to afford 1.1833g (83%) 259 as a brittle, white foam.

NMR(D) (CDCl<sub>3</sub>): 1.11(9H,s); 3.10(3H,s); 3.19(1H,1/2ABq,J=14Hz);  
3.45(3H,s); 3.64(1H,1/2ABq,J=14Hz); 7.01(1H,s);  
7.0-8.0(19H,m).

IR: 1787,1740,1705,1670,1620,1495,1430,1390,1360,1270,1180,  
1160,790,740,705.

Mass Spectrum: 529(2.54); 497(0.81); 439(79.3) 147(39.9);  
135(100), 91(37).

1,4-dimethyl-3-formyl-6-methoxy-6-benzyl-2,5-piperazinedione 260 from  
KF deprotection of 259



To a stirred solution of phthalimido disulfide 259 (0.1776g, 0.25mmol, 1.0eq) in 4mL of 10% aqueous methanol at 0°C was added potassium fluoride (0.0146g, 0.25mmol, 1.0eq). The mixture stirred 15 minutes at 0°C, was poured into pH 7.0 buffer and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered, evaporated and separated on preparative silica gel TLC (eluted with 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to afford 0.0362g (49%) of methoxy enol 260 as white crystals mp 109-111°C (recryst CH<sub>2</sub>Cl<sub>2</sub>).

NMR(A) (CDCl<sub>3</sub>): 2.90(3H,s); 3.13(3H,s); 3.20(2H,s); 3.22(3H,s); 6.57(1H,d,J=11Hz); 6.9-7.5(5H,m); 10.96(1H,exch.,d,J=11Hz).

IR: 3400(broad); 1660, 1590,1455,1410,1390,1240,1180,930, 775,750,730,700.

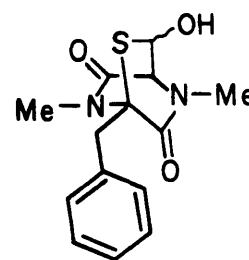
Mass Spectrum: 290(M<sup>+</sup>, 5.99); 258(2.42); 198(100).

Accurate mass measurements:

Calcd. for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: 290.12665  
found: 290.12684

Hemimercaptal 261 from methyldisulfide 246

Methyldisulfide 246 (0.1771g, 0.52mmol) was dissolved in 5mL THF and 5ML methane thiol. A catalytic amount of triethylamine was added and the mixture was stirred at room temperature for 12 hours. Evaporation of the solvents afforded 0.151g (99.4%) of hemimercaptal 261 as an amorphous white powder.



NMR(D) (DMSO-d<sub>6</sub>): 2.73(3H,s); 2.85(3H,s); 3.04(3H,s); 3.12(3H,s); 3.60(4H,s); 4.50(1H,d,J=5Hz); 4.64(1H,d,J=3Hz); 5.59(1H, dd,J=3Hz), J=6Hz); 6.00(1H,dd,J=5Hz, J=4Hz); 6.87(1H,d, J=4Hz); 6.95(1H,d,J=6Hz); 7.2-7.5(10H,m)

IR: 3430,3200,1690,1650,1490,1450,1380,1225,1060,765,750,720 700.

Mass Spectrum: 292(M<sup>+</sup>, 1.24); 230(M-SCHOH)<sup>+</sup>(35.24); 201 (M-C<sub>7</sub>H<sub>7</sub>)<sup>+</sup>(6.47); 91(75.75); 62(SCHOH)<sup>+</sup>(10.58); 42(100).

Accurate mass measurements:

Calcd. for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>S (M)<sup>+</sup>: 292.08816

found: 292.08791

Calcd. for C<sub>14</sub>H<sub>15</sub>N<sub>2</sub>O<sub>3</sub> (M-SH)<sup>+</sup>: 259.10826

found: 259.10865

Calcd. for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> (M-SCHOH)<sup>+</sup>: 230.10552

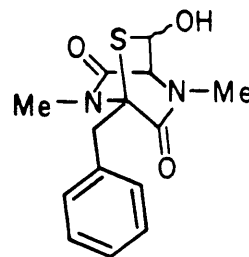
found: 230.10587

Calcd. for C<sub>7</sub>H<sub>9</sub>N<sub>2</sub>O<sub>3</sub>S(M-C<sub>7</sub>H<sub>7</sub>)<sup>+</sup>: 201.03339

found: 201.03398

Hemimercaptal 261 from deprotection  
of thiol 243 with KF

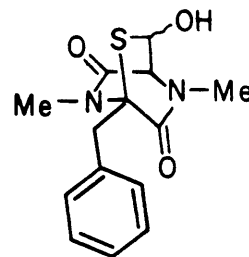
To a stirred solution of thiol 243 (2.0249g, 3.81mmol, 1.0eq) in 10mL THF and 10mL abs. ethanol at 0°C was added potassium fluoride (0.2217g, 3.81mmol, 1.0eq) portionwise. 2mL of methanol was added and the mixture stirred for 30 minutes at 0°C. The resulting bright orange colored solution was acidified with 1.6N HCl in MeOH, poured into a saturated sodium chloride solution and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The residue was triturated with CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O and the product filtered to afford 0.4532g (41%) of hemimercaptal 261 as a white solid. The product so obtained was identical to that obtained from disulfide 246 (see experimental for data).



Hemimercaptal 261 from deprotection

thiol 243 with liquid ammonia

Liquid ammonia (ca 20mL) was condensed into a solution of thiol 243 (0.6397g, 1.2mmol, 1.0eq) in 20mL THF at -78°C. The mixture was stirred



30 minutes at -78°C and the ammonia was allowed to evaporate. The resulting solution was acidified with 1.6N HCl in MeOH, poured into water and extracted thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium sulfate, filtered and evaporated. The residue was triturated with Et<sub>2</sub>O to remove silyl residues, and filtered to afford 0.1267g (36%) of hemimercaptal 261 as a white solid. This material was identical in composition to that obtained from disulfide 246 (see experimental for data).



t-butyldimethylsilyl

hemithioacetal 265 and 264

tert-butyldimethylsilyl chloride

(0.0837g, 0.55mmol, 1.2eq), imidazole

(0.0749g, 1.1mmol, 2.4eq) and hemimercaptal

261 (0.1352g, 0.46mmol, 1.0eq) were stirred

in 0.5mL DMF at room temperature for 12 hours. The solution

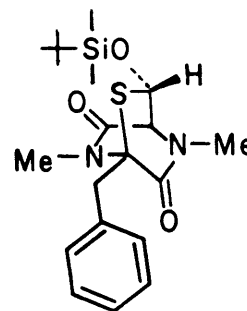
was diluted with CH<sub>2</sub>Cl<sub>2</sub>, poured into water and extracted with

CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous sodium

sulfate, filtered, evaporated and separated on preparative silica

gel TLC (eluted with 1% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to afford 0.0627g (33.5%)

265 and 0.0703g (37.6%) 264. (combined yield 71.1%).



265: NMR(A) (CDCl<sub>3</sub>): 0.00 (3H,s); 0.03 (3H,s); 0.80 (9H,s);

2.67 (3H,s); 3.10 (3H,s); 3.39 (1H,1/2ABq,J=16Hz); 3.69 (1H,

1/2ABq,J=16Hz); 4.31 (1H,d,J=3Hz); 5.56 (1H,d,J=3Hz);

7.22 (5H,s).

IR: (NaCl,neat): 1710,1690,1610,1500,1380,1260,1200,1190,850,

790,710

Mass Spectrum: 391 (M-CH<sub>3</sub>)<sup>+</sup> (0.12); 350 (M-C<sub>4</sub>H<sub>9</sub>)<sup>+</sup> (10.78);

230 (M-SCHOSiC<sub>6</sub>H<sub>15</sub>)<sup>+</sup> (100); 91 (14.85).

Accurate mass measurements:

Calcd. for C<sub>19</sub>H<sub>27</sub>N<sub>2</sub>O<sub>3</sub>SiS(M-CH<sub>3</sub>)<sup>+</sup>: 391.15117

found: 391.14965

Calcd. for  $C_{16}H_{21}N_2O_3SiS(M-C_4H_9)^+$ : 349.10422

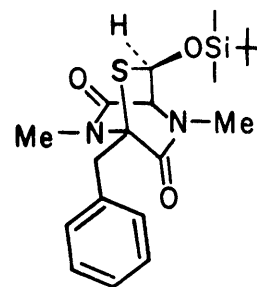
found: 349.10291

Calcd. for  $C_{13}H_{14}N_2O_2(M-SCHOSiC_6H_{15})^+$ : 230.10552

found: 230.10696

Calcd. for  $C_7H_{16}OSiS$ : 176.06912

found: 176.06605



264: NMR(A) ( $CDCl_3$ ): 0.03 (3H, s); 0.11 (3H, s); 0.99 (9H, s);  
2.91 (3H, s); 3.17 (3H, s); 3.55 (2H, s); 4.16 (1H, d,  $J=5$ Hz);  
5.78 (1H, d,  $J=5$ Hz); 7.20 (5Hm).

IR: 1705, 1690, 1500, 1375, 1255, 1110, 1090, 860, 850, 790, 760, 710.

Mass Spectrum: 350 ( $M-C_4H_9$ )<sup>+</sup> (18.02); 230 ( $M-SCHOSiC_6H_{15}$ )<sup>+</sup> (48.8);  
91 (100).

Accurate mass measurements:

Calcd. for  $C_{19}H_{27}N_2O_3SiS(M-CH_3)^+$ : 391.15117

found: 391.15059

Calcd. for  $C_{16}H_{21}N_2O_3SiS(M-C_4H_9)^+$ : 349.10422

found: 349.10566

Calcd. for  $C_{13}H_{23}N_2O_3SiS(M-C_7H_7)^+$ : 315.11987

found: 315.11859

Calcd. for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2(\text{M-SCHOSiC}_6\text{H}_{15})^+$ : 230.10552

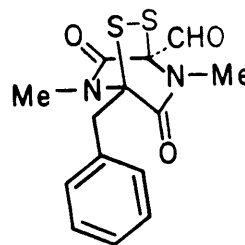
found: 230.10512

Calcd. for  $\text{C}_7\text{H}_{16}\text{OSiS}$ : 176.06912

found: 176.06835

Oxidation<sup>143</sup> of hyalodendrin to  
carboxaldehyde 178

Dimethyl sulfoxide (0.022mL,  
0.308mmol, 2.0eq) is dissolved in  
1.5mL CH<sub>2</sub>Cl<sub>2</sub> at -78°C. Trifluoroacetic  
anhydride (0.032mL, 0.225mmol, 1.5eq) was  
added to the DMSO solution and stirred 3 minutes at -78°C.  
A solution of natural hyalodendrin (50mg, 0.54mmol, 1.0eq)  
in 1.5mL CH<sub>2</sub>Cl<sub>2</sub> was slowly added and the mixture stirred 30  
minutes at -78°C. Triethylamine (0.06mL) was added and stirring  
continued for 30 minutes at -78°C. The mixture was warmed to  
room temperature, poured into water and extracted thoroughly  
with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were dried over anhydrous  
sodium sulfate, filtered and evaporated to afford 0.005g 178  
as a foam. NMR analysis indicated ca. 80% carboxaldehyde  
(aldehyde proton at  $\delta$ 9.84). This compound was not purified.  
The IR also provided evidence for 178: 1740, 1680cm<sup>-1</sup>.



Reduction of crude 178 with sodium borohydride (~50mg)  
in THF/isopropanol for 3 hours at 25° and 30 minutes at reflux  
followed by acidification and oxidation with 2.5% KI<sub>3</sub>·py as  
described for 246 cleanly produced hyalodendrin (TLC).

This is it.  
There are no hidden meanings.  
All that mystical stuff  
is just what's so  
A master is someone who found out.

## References

## References

1. R. Weindling, Phytopathology 22, 837 (1932).
2. J. R. Johnson and J. B. Buchanan, J. Am. Chem. Soc., 75, 2103 (1953).
3. J. R. Johnson, "The Structure of Gliotoxin," in "The Roger Adams Symposium," John Wiley and Sons, Inc., New York, NY., 1955, pp.60-90.
4. M. R. Bell, J. R. Johnson, B. S. Wildi and R. B. Woodward, J. Am. Chem. Soc., 80, 1001 (1958).
5. A. F. Beecham, J. Fridricksons and A. McL. Mathieson, Tetrahedron Lett, 3131 (1966).
6. Reviews: a) A. Taylor, in Microbial Toxins, Academic Press, Inc., New York, 1971; vol. 7, Chapt. 10, p.337; b) P. G. Sammes, Fortschritte der Chemie Organischer Naturstoffe 32, 51 (1975); c) C. Leigh and A. Taylor, Advances in Chemistry Series, No. 149, 1976, p. 228; d) B. Ganem, Tetrahedron, 34, 3353 (1978).
7. D. H. Berg, R. P. Massing, M. M. Hoehn, L. D. Boeck and R. L. Hamill, J. Antibiotics, 394 (1976).
8. A. Kato, T. Saeki, S. Suzuki, K. Ando, G. Tamura and K. Arima, J. Antibiotics, 322 (1969).
9. Sporidesmins Part 1-17: a) R. Rahman, S. Safe and A. Taylor, J. Chem. Soc. Perkin I, 1476 (1978); b) D. Brewer, A. G. McInnes, D. G. Smith, A. Taylor and J. A. Walter, J. Chem. Soc. Perkin I, 1248 (1978); c) J. W. Ronaldson, Aust. J. Chem., 29, 2307 (1976); d) J. W. Ronaldson, Aust. J. Chem. 28, 2043 (1975); e) S. Safe and A. Taylor, J. Chem. Soc.

- Perkin I, 472 (1972); f) E. Francis, R. Rahman, S. Safe and A. Taylor, J. Chem. Soc. Perkin I, 470 (1972);
- g) S. Safe and A. Taylor, J. Chem. Soc. (C), 1189 (1971);
- h) S. Safe and A. Taylor, J. Chem. Soc. (C), 432 (1970);
- i) R. Rahman, S. Safe and A. Taylor, J. Chem. (C), 1665 (1969); j) W. D. Jamieson, R. Rahman and A. Taylor, J. Chem. Soc. (C), 1564 (1969); k) R. Hodges, J. S. Shannon and A. Taylor, J. Chem. Soc. (C), 1803 (1966); l) G. Lowe, A. Taylor and L. C. Vining, J. Chem. Soc. (C), 1799 (1966);
- m) H. Herrmann, R. Hodges and A. Taylor, J. Chem. Soc., 4315 (1964); n) R. Hodges and A. Taylor, J. Chem. Soc., 4310 (1964); o) R. Hodges, J. W. Ronaldson, J. S. Shannon, A. Taylor and E. P. White, J. Chem. Soc., 26 (1964);
- p) R. Hodges, J. W. Ronaldson, A. Taylor and E. P. White, J. Chem. Soc., 5332 (1963).
10. a) D. Hauser, H. P. Weber and H. P. Sigg, Helv. Chim. Acta. 53, 1061 (1970); b) D. Hausaer, H. R. Loosli and P. Niklaus, Helv. Chim. Acta., 55, 2182 (1972); c) H. P. Weber, Acta. Cryst. (B), 28, 2945 (1972).
11. a) K. Katagiri, K. Sato, S. Hayakawa, T. Matsushima and H. Minato, J. Antibiotics, 420 (1970); b) H. Minato, M. Matsumoto, and T. Katayama, J. Chem. Soc. Chem. Comm. 44 (1971); c) H. Minato, M. Matsumoto, and T. Katayama, J. Chem. Soc. Perkin I, 1819 (1973).
12. a) A. D. Argoudelis and F. Reusser, J. Antibiotics, 24(6) 383 (1971); b) A. D. Argoudelis and S. A. Mizzak, J. Antibiotics, 468 (1977).

13. T. Hino, et al, Tetrahedron Lett, 4913 (1978).
14. J. R. Johnson, F. W. Bruce and J. D. Dutcher, J. Am. Chem. Soc., 65, 2005 (1943).
15. W. A. Rightsel, H. G. Schneider, B. J. Sloan, P. R. Graf, F. A. Miller, Q. R. Bartz, J. Ehrlich and G. J. Dixon, Nature, 204, 1333 (1964).
16. P. A. Miller, K. P. Milstrey and P. W. Trown, Science, 159, 431 (1968).
17. R. J. Suhadolnik and R. G. Chenoweth, J. Am. Chem. Soc., 80, 4391 (1958).
18. R. J. Suhadolnik and J. A. Winsted, J. Am. Chem. Soc., 82, 1644 (1960).
19. A. K. Bose, K. G. Das, P. T. Funke, L. Kugadhovsky, O. P. Sukla, K. S. Kanchandani and R. J. Suhadolnik, J. Am. Chem. Soc., 90, 1038 (1968).
20. J. D. Bu' Lock and A. P. Ryles, J. Chem. Soc. Chem. Comm., 1404 (1970).
21. N. Johns and G. W. Kirby, J. Chem. Soc. Chem. Comm. 163 (1971).
22. J. D. Bu' Lock, A. P. Ryles, G. W. Kirby and N. Johns, J. Chem. Soc. Chem. Comm., 100 (1972).
23. G. W. Kirby, G. L. Patrick and D. J. Robins, J. Chem. Soc. Perkin I, 1336 (1978).
24. G. W. Kirby and D. J. Robins, J. Chem. Soc. Chem. Comm. 354 (1976).
25. N. Neuss, R. Nagarajan, B. B. Molloy and L. L. Huckstep, Tetrahedron Letters (42), 4467 (1968).



26. J. D. Bu'Lock and C. Leigh, J. Chem. Soc. Chem. Comm. 628 (1975).
27. D. R. Brannon, J. A. Mabe, B. B. Molloy and W. A. Day, Biochem. Biophys. Res. Comm., 43(3), 588 (1971).
28. G. M. Strunz, M. Kakushima, M. A. Stillwell and C. J. Heissner, J. Chem. Soc. Perkin I, 2600 (1973).
29. G. M. Strunz, C. J. Heissner, M. Kakushima and M. A. Stillwell, Can. J. Chem., 52, 325 (1974).
30. G. M. Strunz, M. Kakushima and M. A. Stillwell, Can. J. Chem., 53, 295 (1975).
31. M. A. Stillwell, L. P. Magasi, and G. M. Strunz, Can. J. Microbiol., 20, 579 (1974).
32. R. L. DeVault and W. Rosenbrook, J. Antibiotics, 532 (1973).
33. K. H. Michel, M. O. Chaney, N. D. Jones, M. M. Hoehn and R. Nagarajan, J. Antibiotics, 27(1), 57 (1974).
34. F. Dorn and D. Arigoni, Experientia, 30(2), 134 (1974).
35. R. L. DeVault, U. S. Pat. 3,715,352.
36. Hyalodendrons/sp was found as a contaminant on a malt agar plate in Fredericton, New Brunswick by Strunz, et al while screening for microorganisms showing antagonism to the growth of fungi affecting wood products, as well as certain tree pathogens.
37. S. A. Waksman and E. Bugie, J. Bacteriol., 48, 527 (1944).
38. S. Safe and A. Taylor, J. Chem. Soc. Perkin I, 472 (1972).
39. A. G. McInnes, A. Taylor and J. A. Walter, J. Am. Chem. Soc., 98, 6741 (1976).

40. D. Brewer, A. G. McInnes, D. G. Smith, A. Taylor and J. A. Walter, J. Chem. Soc. Perkin I, 1248 (1978).
41. R. Baute, G. Deffieux, M.-A. Baute, M.-J. Filleau and A. Neveu, Tetrahedron Lett. (44), 3943 (1976).
42. M.-A. Baute, G. Deffieux, R. Baute and A. Neveu, J. Antibiotics, 31(11), 1099 (1978).
43. G. Deffieux, M.-J. Filleau and R. Baute, J. Antibiotics, 31(11), 1106 (1978).
44. G. Deffieux, M.-A. Baute, R. Baute and M.-J. Filleau, J. Antibiotics, 31(11), 1102 (1978).
45. D. H. Berg, R. P. Massing, M. M. Hoehn, L. D. Boeck and R. L. Hamill, J. Antibiotics, 394 (1976).
46. A. Kato, T. Saeki, S. Suzuki, K. Ando, G. Tamura and K. Arima, J. Antibiotics, 322 (1969).
47. P. J. Curtis, D. Greatbanks, B. Hesp, A. F. Cameron and A. A. Freer, J. Chem. Soc. Perkin I, 180 (1977).
48. J. P. Ferezou, C. Riche, A. Q.-Thierry, C. P.-Billy, M. Barbier, J. F. Bousquet and G. Boudart, Nouveau J. Chim., 1(4), 327 (1977)
49. W. H. Rastetter and L. J. Nummy, Tetrahedron Lett. in press.
50. A. R. Gregory and M. Przybylska, J. Am. Chem. Soc., 100(3), 943 (1978).

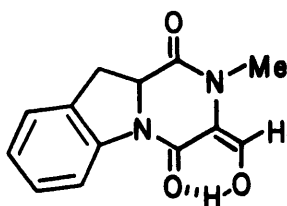
51. R. Steudel, Angew. Chem. Int. Ed. 14 (10), 655 (1975).
52. R. P. Sajewski and G. M. Whitesides, J. Am. Chem. Soc.  
in press.
53. J. D. M. Herscheid, M.W. Tijhuis, J. H. Noordik and  
H. C. J. Ottenheijm, J. Am. Chem. Soc., 101 (5), 1159  
(1979).
54. Y. Kishi, Pure Appl. Chem., 43, 423 (1975).
55. a) R. Nagarajan, L. L. Huckstep, D. H. Lively, D. C. DeLong,  
M. M. Marsh and N. Neuss, J. Am. Chem. Soc., 90, 2980 (1968);  
b) J. W. Moncrief, J. Am. Chem. Soc., 90 (23), 6517 (1968);  
c) D. B. Cosulich, N. R. Nelson and J. H. van den Hende,  
J. Am. Chem. Soc., 90 (23), 6518 (1968).
56. J. D. Dutcher, J. R. Johnson and W. F. Bruce, J. Am. Chem.  
Soc., 67, 1736 (1945).
57. R. Nagarajan and R. W. Woody, J. Am. Chem. Soc., 95 (22),  
7212 (1973).
58. P. W. Trown, Biochem. Biophys. Res. Comm., 33 (3), 402 (1968).
59. T. Fukuyama, Ph. D. thesis, Harvard University, Department  
of Chemistry, 1977.
60. J. Yoshimura, Y. Sugiyama and H. Nakamura, Bull. Chem.  
Soc. Jap., 46, 2850 (1973).
61. J. Yoshimura, H. Nakamura, K. Matsunari and Y. Sugiyama.  
Chem. Lett., 559 (1974).
62. H. Poisel and U. Schmidt, Chem. Ber., 104, 1714 (1971).
63. H. Poisel and U. Schmidt, Angew. Chem. Int. Ed., 10 (2),  
130 (1971).

64. E. Öhler, F. Tataruch and U. Schmidt, Chem. Ber., 106, 165 (1973).
65. H. Poisel and U. Schmidt, Chem. Ber., 105, 625 (1972).
66. E. Öhler, H. Poisel, F. Tataruch and U. Schmidt, Chem. Ber., 105, 635 (1972).
67. E. Öhler, F. Tataruch and U. Schmidt, Chem. Ber., 105, 3658 (1972).
68. E. Öhler, F. Tataruch and U. Schmidt, Chem. Ber., 106, 165 (1973).
69. E. Öhler, F. Tataruch and U. Schmidt, Chem. Ber., 106, 396 (1973).
70. J. Hausler and U. Schmidt, Chem. Ber., 107, 2804 (1974).
71. a) E. Öhler and U. Schmidt, Chem. Ber. 108, 2907 (1975);  
b) H. Poisel and U. Schmidt, Chem. Ber., 108, 2917 (1975).
72. H. C. J. Ottenheijm, G. P. C. Kerkhoff, and J. W. H. A. Bijen, J. Chem. Soc. Chem. Comm., 768 (1975).
73. H. C. J. Ottenheijm, J. D. M. Herscheid, G. P. C. Kerkhoff and T. F. Spande, J. Org. Chem., 41 (21), 3433 (1976).
74. a) H. C. J. Ottenheijm, J. D. M. Herscheid, M. W. Tijhuis and M. Oosterbaan, J. Med. Chem., 21 (8), 79 (1978);  
b) H. C. J. Ottenheijm, J. D. M. Herscheid, M. W. Tijhuis and R. J. F. Nivard, J. Med. Chem., 21 (8), 799 (1978).
75. U. Schmidt, J. Hausler, E. Ohler and H. Poisel, Chem. Ber., 110, 3722 (1977).
76. H. C. J. Ottenheijm, Chem. Ber., 111, 2064 (1978).

77. H. C. J. Ottenheijm, T. F. Spande and B. Witkop, J. Am. Chem. Soc., 95 (6), 1989 (1977).
78. H. C. J. Ottenheijm, A. D. Potman and T. van Vroonhoven, Rec. Trav. Chim., 94, 135 (1975).
79. An x-ray analysis of 118 along with an unusual dimer derived from 118 show a boat conformation for 118, thus supporting the proposed  $\text{Zn}^{+2}$  chelate in 119; J. H. Noordik, K. D. M. Herscheid, M. W. Tijhuis and H. C. J. Ottenheijm, Rec. Trav. Chim., 97 (4), 91 (1978).
80. T. Hino and T. Sato, Tetrahedron Lett., 3127 (1971).
81. T. Hino and T. Sato, Chem. Pharm. Bull., 22, 2866 (1974).
82. T. Sato and T. Hino, Tetrahedron, 32, 507 (1976).
83. D. L. Coffen, D. A. Katonak, N. R. Nelson and F. D. Sancilio, J. Org. Chem., 42 (6), 948 (1977).
84. U. Schmidt, Pure and Appl. Chem., 49, 163 (1977) and refs. therein.
85. P. M. Pojer and I. D. Rae, Tetrahedron Lett., 3077 (1971)
86. A. Kaneda and R. Sudo, Bull. Chem. Soc. Jap., 43, 2159 (1970).
87. S. M. Patel, J. O. Currie and R. K. Olsen, J. Org. Chem., 38, 126 (1973).
88. J. Yoshimura and Y. Sugiyama, Bull. Chem. Soc. Jap., 45, 1554 (1972).
89. J. Hausler and U. Schmidt, Monats. Chem., 109, 147 (1978).
90. J. Hausler, R. Jahn and U. Schmidt, Chem. Ber., 111, 361 (1978).

91. E. Öhler, E. Prantz and U. Schmidt, Chem. Ber., 111, 1058 (1978).
92. a) P. J. Machin and P. G. Sammes, J. Chem. Soc. Perkin I, 698 (1974); b) idem., ibid. 624 (1976); c) idem. ibid., 628 (1976).
93. I. L. Karle, H. C. J. Ottenheijm and B. Witkop, J. Am. Chem. Soc., 96 (2), 539 (1974).
94. T. Petrzilka and Ch. Fehr, Helv. Chim. Acta, 56 (4), 1218 (1973).
95. T. F. Schlaf, Ph. D. thesis, Northwestern University, Department of Chemistry, 1974.
96. J. A. Marshall, T. F. Schlaf and J. G. Csernansky, Synthetic Comm., 5 (3), 237 (1975).
97. H. C. J. Ottenheijm, N. P. E. Vermeulen and L. F. J. M. Breuer, Liebigs Ann. Chem., 206 (1974).
98. H. C. J. Ottenheijm, J. A. M. Hulshof, and R. J. F. Nivard, J. Org. Chem., 40 (15), 2147 (1975).
99. M. Ohno, T. F. Spande and B. Witkop, J. Am. Chem. Soc., 92, 2 (1970).
100. Y. Kishi, T. Fukuyama and S. Nakatsuka, J. Am. Chem. Soc., 95 (19), 6490 (1973).
101. idem., ibid., 95 (19), 6492 (1973).
102. Y. Kishi, S. Nakatsuka, T. Fukuyama and M. Havel, J. Am. Chem. Soc., 95 (19), 6493 (1973).
103. S. Nakatsuka, T. Fukuyama and Y. Kishi, Tetrahedron Lett. 1549 (1974).

104. T. Fukuyama, S. Nakatsuka and Y. Kishi, Tetrahedron Lett. 3393 (1976).
105. T. F. Fukuyama and Y. Kishi, J. Am. Chem. Soc., 98, 6723 (1976).
106. G. M. Strunz and M. Kakushima, Experientia, 30, 719 (1974).
107. K. Sasaki, T. Fukuyama, S. Nakatsuka and Y. Kishi, J. Chem. Soc. Chem. Comm., 542 (1975).
108. J. E. Ellis, J. H. Fried, I. T. Harrison, E. Rapp and C. H. Ross, J. Org. Chem., 42, 2891 (1977).
109. K. C. Murdock, J. Med. Chem., 17 (8), 827 (1974).
110. M. V. Kalnins, Can. J. Chem., 44, 2111 (1966).
111. K. S. Boustany and A. B. Sullivan, Tetrahedron Lett., 3547 (1970).
112. D. N. Harpp, D. K. Ash, T. G. Back, J. G. Gleason, B. A. Orwig and W. F. VanHorn, Tetrahedron Lett., 3551 (1970).
113. D. N. Harpp and T. G. Back, Tetrahedron Lett., 1481 (1972).
114. a) D. N. Harpp and D. K. Ash, Int. J. Sulfur Chem. A, 1 (1), 57 (1971); b) idem. ibid., 1 (3), 211 (1971).
115. S. Masson, M. Saquet and A. Thuiller, Tetrahedron, 33, 2949 (1977).
116. H. Viola and R. Mayer, Z. Chem., 15, 348 (1975).
117. W. S. Johnson and H. Posvic, J. Am. Chem. Soc., 69, 1361 (1947).
118. After most of the synthetic work described in Chapter 3 was complete, it came to my attention that J. A. Marshall and T. Schlaf<sup>95</sup> had prepared i by formulation of the



i

corresponding diketopiperazine. The yield of their procedure was low (25%) and they found that i readily reverted back to starting material. No further transformations of i were reported.

119. D. N. Harpp, K. Steliou and T. H. Chan, J. Am. Chem. Soc., 100, 1222 (1978).
120. T. Kumamoto, S. Kobayashi and T. Mukuyama, Bull. Chem. Soc. Jap., 45, 866 (1972).
121. T. Mukuyama, S. Kobayashi and T. Kumamoto, Tetrahedron Lett., 5115 (1970).
122. F. A. Davis, Org. Prep. and Proc. Int., 11 (1), 33 (1979).
123. J. J. D'Amico and W. E. Dahl, J. Org. Chem., 40 (9), 1224 (1975).
124. D. Seebach and M. Teschner, Chem. Ber. 109, 1601 (1976).
125. H. Brintzinger, K. Pfannstiel, H. Koddebusch and K. E. Kling, Chem. Ber., 83, 87 (1950).
126. E. J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 94 (17), 6190 (1972).
127. An authentic sample of bis-dethio(methylthio)hyalodendrin (antipode of gliovictin) was kindly furnished by Dr. George M. Strunz of the Canadian Forestry Service. Dr. Strunz also kindly provided a sample of natural



128. A related observation was reported by T. Fukuyama; see ref. 59.
129. P. G. Sammes, Chem. Rev., 76 (1), 113 (1976).
130. a) C. T. Buse and C. H. Heathcock, J. Am. Chem. Soc., 99, 8109 (1977); b) W. A. Kleschick, C. T. Buse, and C. H. Heathcock, J. Am. Chem. Soc., 99, 247 (1977).
131. R. Williams and W. H. Rastetter, Tetrahedron Lett., (14), (1979).
132. As a check on the stability of the phthalimido disulfide functionality, prolylproline phthalimido disulfide 164 was subjected to the same hydrolysis conditions. Significant decomposition resulted; the mixture of products was devoid of the phthalimido group.
133. a) Y. Kishi, S. Nakatsuka, T. Fukuyama and T. Goto, Tetrahedron Lett., 4657 (1971); b) N. Takamatsu, S. Inoue and Y. Kishi, ibid., 4661 (1971); c) idem. ibid., 4665 (1971).
134. For reviews on the anomeric effect, see: a) R. U. Lemieux, Pure Appl. Chem., 25, 527 (1971); b) E. L. Eliel, Angew. Chem. Int. Ed., 11, 739 (1972); see also: c) A. Abe, J. Am. Chem. Soc., 98, 6477 (1976); d) F. A. L. Anet and I. Yavari, J. Am. Chem. Soc., 99, 6752 (1977).
135. L. Field and B. J. Sweetman, J. Org. Chem., 34, 1799 (1969).
136. W. C. Still, M. Kahn and A. Mitra, J. Org. Chem., 43, 2923 (1978).

137. W. G. Kofron and L. M. Baclawski, J. Org. Chem., 41, 1879 (1976).
138. J. Kapfhammer and A. Matthes, Z. Physiol. Chem., 223, 43 (1934).
139. A. Chemizard and S. David, Bull. Chem. Soc. Fr., 184 (1965).
140. S. Hanessian and P. Lavallee, Can. J. Chem., 53, 2975 (1975).
141. G. E. Lienhard and W. P. Jencks, J. Am. Chem. Soc., 88, 3982 (1966).
142. Ring formation favors hemimercaptal formation; as an example, a stable 5-membered cyclic hemimercaptal was prepared by Woodward and co-workers in "The Synthesis of Cepalosporin C", R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan and H. Vorbruggen, J. Am. Chem. Soc., 88, 852 (1966).
143. S. L. Huang, K. Omura and D. Swern, J. Org. Chem., 41 (20), 3329 (1976).

ACCREDITATIONS

The quote on the "Acknowledgement" page is by Robert Pirsig, from "Zen and the Art of Motorcycle Maintenance,"

The X-ray structures on page 32 are from ref. 50.

The structure on the "Total Syntheses" page is from ref. 103.

The quote on pages 64 and 190 are by Werner Erhard.

The X-ray stereogram on page 72 is from ref. 33.

The quote on the "Experimental" page is by Don Juan. from "Journey to Ixtlan" by Carlos Castenada.

## BIOGRAPHICAL SKETCH

The whole universe is COMPLETELY INSANE.

Mr. Natural

BIOGRAPHICAL SKETCH

Robert Michael Williams was born on February 8, 1953 in Queens, New York. He was raised and received his secondary education in Huntington, Long Island, New York. Being the son of a pharmacist and bacteriologist, the author became interested in sciences during high school. However, it was not until 1971 when he entered college at Syracuse University that he became interested in chemistry. As an undergraduate, the author was involved in organoboron research under the supervision of Professor Ei-ichi Negishi. He completed his Bachelor's thesis on "A Stereoselective Synthesis of 1,2,3-Butatriene Derivatives..." and graduated summa cum laude with highest distinction in Chemistry on May 10, 1975. The author was also awarded the Kanner Prize in Chemistry and Physics at Syracuse University. After marrying Janet W. Reisinger on May 11, 1975, the author came to M.I.T. and began his graduate studies with Professor William H. Rastetter.

The author has accepted a postdoctoral position at Harvard University with Professor Robert B. Woodward.

PUBLICATIONS

A Stereoselective Synthesis of Partially Substituted  
1,2,3-Butatriene Derivatives via Hydroboration

T. Yoshida, R. M. WILLIAMS and E. Heghishi,  
J. Am. Chem. Soc., 96, 3688 (1974).

A Stereoselective Synthesis of cis-Alkenylboranes

E. Negishi, R. M. WILLIAMS, G. Lew and T. Yoshida,  
J. Org. Met. Chem., 92, C4-C6 (1975).

An Efficient Synthesis of d,l-Gliovictin: Construction  
of the Hydroxymethyl Moiety via a 3-Formyl-2,5-Piperazinedione

R. M. WILLIAMS and W. H. Rastetter,  
Tetrahedron Lett. (14), 1187 (1979).